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CHEMOTHERAPY OF MALARIA

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INTRODUCTION

At its fourth session, held in Kampala, Uganda, in December 1950, the Expert Committee on Malaria of the World Health Organization expressed the opinion that it was desirable to bring together for the benefit of the medical profession factual information on the properties of antimalarial drugs, and advised the appointment of a drafting committee to undertake the task In accordance with this recommendation, a committee was appointed with the following members Sir Gordon Covell (Chairman), Dr G Robert Coatney, Dr John W Field, and Lieutenant Colonel Jaswant Singh

The fact that the four members of the committee are resident in countries as far distant from one another as England, the United States of America, Malaya, and India has necessarily delayed the completion of the work It has not been possible for the entire committee to meet at any one time during the preparation of the text, but the Chairman has been able to hold personal discussions from time to time with Dr Coatney and Dr Field and has maintained contact with Lieutenant Colonel Jaswant Singh by correspondence

The committee wishes to acknowledge with thanks the assistance received from Dr W Clark Cooper and Dr Howard W Bond, USA, Dr T Wilson and Dr J F B Edeson, Malaya, and Dr A P Ray and Dr H L Bami of the Malaria Institute of India, Delhi

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CHAPTER 1

DEFINITION OF TERMS AND HISTORICAL REVIEW

Definition of Terms

The terminology followed in this study is in conformity with that suggested in the monograph *Malaria terminology*,[1] issued by the World Health Organization in 1953, viz

Blood schizontocide * a drug which acts on asexual parasites in the blood

Tissue schizontocide a drug which acts on asexual parasites in the tissues

(a) *primary tissue schizontocide* a drug which acts on pre-erythrocytic (primary exoerythrocytic) forms,

(b) *secondary tissue schizontocide* a drug which acts on secondary exoerythrocytic forms

Gametocytocide a drug which acts on the sexual forms of the parasite

Sporontocide a drug which acts on the sporogonic forms in the mosquito

Suppression implies the prevention of clinical symptoms by action on asexual parasites in the blood It may be *temporary*, that is, operative only while the drug is being taken, or *permanent*, denoting that no attack will supervene even after the drug has been discontinued

Clinical cure indicates that the immediate symptoms of an attack have been relieved and that the patient has apparently recovered

Radical cure implies elimination of the parasite from the body, whether by natural recovery or as the result of treatment

Suppressive cure implies radical cure brought about while the patient is receiving suppressive medication

Spontaneous recovery is a term applied to clinical or radical cure brought about by nature, in the absence of specific medication

The word *prophylaxis* is commonly used for any method of protection from disease and, therefore, when applied to chemotherapy, it should

* This word is sometimes spelt *schizonticide* which is etymologically incorrect it is generally accepted that if the first element of a compound word is Greek the letter o is inserted before the suffix if Latin the letter i

properly be designated *drug prophylaxis* When applied to a community, the term *collective drug prophylaxis* is used, when to an individual, the term *individual drug prophylaxis* *Clinical drug prophylaxis* is a term sometimes applied when the object is merely to prevent the occurrence of overt attacks during such time as the drug is administered Action on the asexual erythrocytic forms is, however, already covered by the word suppression, and it is suggested that the word prophylaxis when applied to chemotherapy should be restricted to action on sporozoites or other pre erythrocytic forms (equivalent to the *true causal* or *causative prophylaxis* of James)

Names of antimalarial drugs ending with "in(e)" are written with an "e" by some authors and without an "e" by others For the sake of uniformity, in this monograph all such words, unless they are trade names, are written with an "e", for example, chloroquine, amodiaquine, pamaquine, mepacrine, primaquine In proprietary names of drugs a capital is used for the initial letter, in non proprietary names the initial letter is given in lower case

Historical Review

Before the outbreak of the first World War, the only specific antimalarial drugs known were the cinchona alkaloids, of which the most commonly used was quinine

Cinchona is the name given by Linnaeus to a family of plants indigenous to the eastern slopes of the Andes in memory of the Countess of Chinchon, wife of an early Viceroy of Peru, to whom legend attributes the introduction of the bark to Europe Historical evidence does not support this story, but it is a fact that the bark of the *quina quina* tree, now known as cinchona, was introduced into Europe from South America by the Spaniards about the year 1640, and was used in Spain and Italy for the treatment of fevers from that time onward Powdered bark had reached England by 1655 and was prescribed as such for the treatment of intermittent fevers for the next 200 years It was used in North America during the War of Independence by the troops of both the contending armies

The bark is said to have been introduced into India as early as 1657 During the latter half of the 18th century it was used extensively in that country, where it was popularized by the surgeons of the numerous ships trading in eastern waters Dr James Lind treated over 400 cases of intermittent or remittent fever in Bengal with cinchona bark in the year 1765 with excellent results In the first half of the 19th century, cinchona passed through a phase of unpopularity in India, principally due to the malign influence of a certain Dr Johnson, a naval surgeon, who visited Calcutta in 1804 He treated his first fever patient with cinchona bark and failed

to effect a cure He bled and purged his second patient, who recovered, and thenceforth advocated a line of treatment of which the main feature was drastic purgation, salivation, and venesection After a brief sojourn in India he returned to England, where he published a treatise on tropical diseases in which the administration of cinchona bark as a remedy for malaria was vehemently condemned As a result, the use of the bark in India was practically abandoned, and for many years it was used merely as a tonic, in minute doses, after the subsidence of the fever At this period as much as from 800 to 900 grains (50-60 g) of calomel were commonly prescribed for the treatment of a single attack of malaria

From about the middle of the 19th century, the popularity of cinchona bark was re-established, largely through the influence of Edward Hare, who came to India in 1839 and was in medical charge of British troops in the Burmese War and during the siege of Delhi at the time of the Indian Mutiny At this time the use of cinchona bark for malaria was frowned upon by the authorities, but Hare came across some of the old writings of James Lind, extolling its virtues, and decided to give it a trial Over a period of nine years he treated some 7,000 cases of fever, with a mortality of less than ½%

In 1820, quinine and cinchonine were isolated from the bark by two French scientists, Caventou and Pelletier The dominant position subsequently attained by quinine in the treatment of malaria as compared with the other alkaloids of cinchona was largely due to the fact that it was the first to be isolated In point of fact there is little difference as regards antimalarial properties between it and the three other principal alkaloids present

Cinchona cultivation was established in Java by the Dutch in 1854, with seedlings brought from Bolivia and Peru by the botanist Hasskarl In 1860, the British geographer Clements Markham obtained seeds from Peru, from which plantations were stocked in India and Ceylon, where the industry flourished for a while, but during the period 1880-90 reckless over production led to a fall in prices which proved ruinous The planters in Java managed to survive the slump, and at the outbreak of the second World War about 97% of the world s supply of quinine came from that country

The evolution of the synthetic antimalarials now in use makes an interesting story [8] Quinine is an effective drug for treatment of the clinical attack in most malarial infections, and it is doubtful whether any of the synthetic antimalarials would have been evolved but for the occurrence of the two World Wars The fact that the Germans were cut off from all sources of quinine during the first World War was the stimulus which inspired the *intensive search for synthetic substitutes which resulted in the*

production of Plasmochin (now known as pamaquine) and later of Atebrin (now known as mepacrine) When this work was planned in the early 1920s, all attempts to synthesize quinine had failed, this was finally accomplished in 1944 [32] But Guttmann & Ehrlich,[14] in 1891, had discovered that methylene blue effectively stains malaria parasites and had tried the dye on patients suffering from vivax malaria, some of whom were relieved of their symptoms The results were not sufficiently impressive to warrant the substitution of methylene blue for quinine, but they were destined to play an important part in shaping the course of subsequent researches

In their work at Elberfeld,[23] the Bayer research chemists were greatly helped by a technique of testing antimalarial compounds in canaries infected with *Plasmodium relictum*, this system for evaluating compounds was introduced by Roehl in 1924 With Ehrlich's early observations in mind, they introduced a basic side chain into the formula of methylene blue, an easier procedure than effecting similar alterations in the quinine structure One of the resulting compounds showed considerable activity against bird malaria The next step was to attach various side chains to the quinoline nucleus, which is present in quinine This line of approach finally resulted in the synthesis of pamaquine, which in 1925 was selected for clinical investigation from a large number of allied compounds Pamaquine thus became the first synthetic quinoline compound to exhibit effective action against human malaria parasites, and the first drug of any sort with a destructive effect on the gametocytes of *P falciparum*

Although pamaquine has remarkable antimalarial properties, it was unsuitable as a therapeutic agent in several respects, the most important being its relatively high toxicity and the fact that it has little action on the asexual erythrocytic forms of *P falciparum* The German scientists accordingly embarked on further studies They attached the basic side-chain which had been evolved for pamaquine to other heterocyclic nuclei, and in 1930 finally produced the acridine compound now known as mepacrine This proved to be relatively non toxic and was the first synthetic drug with a definite destructive action on the asexual blood forms of *P falciparum* Approximately 12,000 different compounds were tested in the course of this work

After preliminary tests on human malaria in Germany, pamaquine and mepacrine were subjected to an extensive series of field trials in various parts of the world under the auspices of the League of Nations These trials, made in Algeria, Italy, Malaya, Roumania, and the USSR, brought clear and decisive proof of the high suppressive action of mepacrine in all forms of human malaria, but left some uncertainty as to the possible toxic effects of long-continued administration Sinton & Bird [31] in India made the unexpected discovery that pamaquine caused a *marked reduction in*

the relapse rate of vivax malaria—a finding of fundamental importance in subsequent researches on the 8-aminoquinolines. The protective properties of both pamaquine and mepacrine were studied by James and his colleagues in England. Pamaquine proved to be a causal prophylactic against *P. falciparum* and a partial causal prophylactic in vivax infections, though only at a dosage dangerously high for routine use. Mepacrine in a daily dosage of 100 mg was shown to be an effective suppressant for both vivax and falciparum infections, but at that time fears were expressed that this amount taken over an extended period might exert a harmful action.

The Germans went on to synthesize two other compounds, Resochin (chloroquine) and Sontochin (sontoquine). Chloroquine was synthesized as early as 1934, but after a few human tests it was discarded on the ground that it was too toxic. Sontoquine, with its extra CH_3 group, was later produced in an attempt to neutralize these effects, and was undergoing field trials when the second World War broke out in 1939.

In the second World War, the Allies in their turn were cut off from the main sources of quinine when the Japanese overran Indonesia, and an enormous volume of research on antimalarials was undertaken on both sides of the Atlantic. In the United States of America an intensive investigation of the absorption, distribution, excretion, and metabolic transformation of mepacrine was undertaken. By mid-1943, it was shown that the drug was extensively localized in the tissues and that its effectiveness was a function of the concentration in the plasma. This information led to the adoption of improved dosage schedules and its general acceptance as an effective therapeutic agent in the management of malaria. The properties of mepacrine were explored, though on a very much less extensive scale, in the United Kingdom.

In Australia, during the period 1943-5, an extensive series of tests, in which more than 800 volunteers from military units took part, was conducted by an Army medical research team.[7] These tests confirmed and amplified the earlier work on the suppressive value of mepacrine, and also proved that a daily dose of 100 mg of the drug could be continued for an indefinite period without serious ill-effects. It was the routine use of mepacrine as a suppressant, based on these findings, which enabled the Allied armies in the south-west Pacific and south-east Asia commands to be maintained in a fighting condition at a time when the Japanese troops opposing them were gravely hampered by malaria casualties.

The French in North Africa studied the properties of sontoquine, established its high antimalarial activity, and found that it was well tolerated. Following the occupation of North Africa by the Allies, this information became available to the United States investigators, who synthesized a large series of 4-aminoquinoline derivatives, nine of which were given limited

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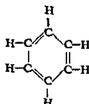
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Graphic formulae



benzene ring



pyridine ring



pyrimidine ring



quinoline ring



acridine ring

Certain arsenical compounds, such as Stovarsol and Salvarsan, which have some action in vivax malaria, are benzene derivatives The quinoline ring has much greater importance, and is the basis of the principal cinchona alkaloids and of the 4-amino- and 8 aminoquinolines The acridine ring is the basis of mepacrine, chloroquine may be regarded as mepacrine with one ring removed, sontoquine and amodiaquine are modifications of chloroquine Quinine is a 6 methoxyquinoline, while pamaquine, pentaquine, isopentaquine, and primaquine are 6-methoxy-8 aminoquinolines, that is, they are quinoline derivatives with a methoxy or amino group at the sixth or eighth position of the quinoline nucleus, counting from the nitrogen atom In proguanil, the benzene ring is attached to a biguanide chain, pyrimethamine is a substituted pyrimidine

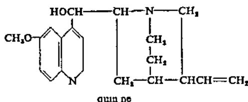
Cinchona alkaloids

Cinchona contains more than 20 alkaloids, but only four are of importance quinine, quinidine, cinchonine, and cinchonidine Cinchona febrifuge and totaquine are mixtures of alkaloids derived from the bark, the difference between them being that samples of the former may vary in composition, while in the latter the percentage of total crystallizable alkaloids and the quinine content must conform to a prescribed standard

Chemically, quinine is a compound of complex molecular structure, visualized as being made up of three parts the *quinoline component* (6-methoxyquinoline), the quinuclidine part (a complex ring with an attached vinyl group), and the connecting link (a hydroxylated methylene

group) Quinidine is an optical isomer of quinine, cinchonine and cinchonidine are optical isomers lacking the methoxy group

Graphic formula



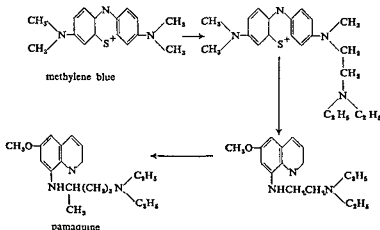
quinine

Various minor modifications of quinine have been studied in an attempt to evolve more active compounds but none of them has proved of practical value for the treatment or prophylaxis of human malaria

8 aminoquinolines

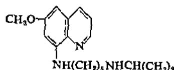
Mention has already been made of the early German researches in which methylene blue was shown to have some inhibitory effect on plasmodia Schulemann and his colleagues at Elberfeld [23] found that by replacement of one of the methyl groups of methylene blue with a basic dialkylaminoalkyl group antimalarial activity was considerably enhanced It seemed likely that the activity of the quinoline nucleus present in quinine might also be increased by the introduction of a similar basic side chain It was by this line of reasoning that, in 1924, pamaquine was evolved

Graphic formulae



Pentaquine, isopentaquine, and primaquine, evolved as the result of re-examination of the 8 aminoquinolines in the United States of America during and after the second World War, differ from pamaquine in the type of alkylamino chain attached to the 6-methoxyquinoline ring

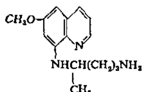
Graphic formulae



pentaquine



isopentaquine



primaquine

9-aminoacridines

Mepacrine is an acridine dye, in which the quinoline ring is broadened to form the acridine In the hope of decreasing toxicity, the German scientists replaced the quinoline ring of pamaquine by the acridine, which is relatively closely related to quinoline By introducing the chlorine atom and a methoxy group into the acridine ring they finally produced mepacrine, in which the side chain is opposite the ring nitrogen as in quinine It has been suggested that the activity of mepacrine is due to the capacity of the molecule to exhibit a form of tautomerism involving the lability of a hydrogen atom which can assume two alternative positions in the molecule

Graphic formula



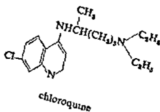
mepacrine

4 aminoquinolines

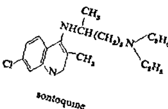
Studies carried out in Germany on this group of compounds followed the work on pamaquine and mepacrine in logical sequence The mepacrine molecule was broken down into its constituent parts in an attempt to throw further light on the relationship between chemical structure and antimalarial activity The removal from mepacrine of the methoxy bearing ring gave rise to chloroquine (originally known as Resochin) As already noted, sontoquine differs from chloroquine in having an extra methyl group on the quinoline nucleus

Another member of the group, amodiaquine (Camoquin), in which the alkylamino side chain is replaced by a substituted anilino group, has also proved to be an effective blood schizontocide These three drugs, together with mepacrine and quinine, all bear a structural similarity to one another All except mepacrine are quinolines, and mepacrine may be regarded as containing the quinoline nucleus, and all have side chains opposite the ring nitrogen It is probable that they all have a similar fundamental action against malaria parasites

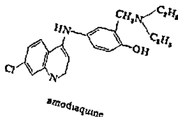
Graphic formulae



chloroquine



sontoquine



amodiaquine

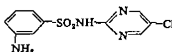
Sulfonamides

Since Diaz de León [8] in 1937 first claimed to have successfully treated cases of vivax malaria with a sulfa compound, many of these have been tested against avian, simian, and human malaria Although none of the

group has proved of practical value in the chemotherapy of malaria, these studies have helped to elucidate a number of problems and have served as a guide in the synthesis of other compounds Sulfanilamide will cure blood-induced knowlesi malaria, and many other derivatives of sulfanila-
mide, such as ct as true causal prophy-
lactics against while the fact that the
antimalarial ac by *p* aminobenzoic acid
has shed light on the metabolic requirements of plasmodia generally

One of the sulfonamides—metachloridine, which is structurally similar to sulfadiazine—is said to be active against quartan malaria, but against falciparum infections it has proved ineffective

Graphic formula



metachloridine

Biguanides

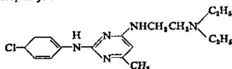
The work which led to the recognition of the antimalarial properties of this group of drugs began with the investigation by Curd, Davey & Rose [964] of certain pyrimidine derivatives, prompted by a consideration of the antimalarial activity of the pyrimidine-substituted sulfanilamides A *second reason for studying the pyrimidines was the similarity between* the formulae of mepacrine and riboflavine, it was thought that the activity of mepacrine might be due to a competition with riboflavine for certain enzyme systems in the malaria parasite A third reason was the characteristic of resonance * possessed both by the pyrimidines and by mepacrine

In these researches the first compound found to be really active against bird malaria was number 2666 This compound contains the substituted pyrimidine ring and an alkylamino group attached to a nitrogen atom, close inspection of the formula shows both extended and true amidine systems Another compound, 3349, a guanidine derivative of 2666, is even richer in amidine groups, it was the first of the series to show activity *against human malaria* This *compound* is capable of existing in several tautomeric forms, and it therefore seemed possible that a pyrimidine ring as such was not essential and could be substituted by a biguanide group, which is capable of similar tautomerism *Eventually, the highest activity*

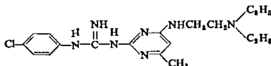
* Resonance is the phenomenon due to the transition from an electron configuration into another of the same spatial nuclear structure in a molecule *It is also called mesomerism* and must not be confused with tautomerism in which the spatial arrangement of the atomic nuclei is different for the two tautomers —ED

in place of the more complex diethylaminoethyl group

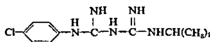
Graphic formulae



2666 RP



3349 RP



proguanil

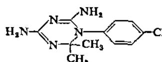
Diaminopyrimidines

Hitchings and his colleagues in the United States of America found that several substituted diaminopyrimidines are powerful antagonists of pteroylglutamic acid in cultures of *Lactobacillus casei* The formal analogy between 2 4-diamino-5 *p*-chlorophenoxypyrimidine and proguanil and the finding that proguanil was also an antagonist of pteroylglutamic acid suggested that the pyrimidine compound might have antimalarial activity A number of members of the group were studied and it was found that those with a 5 phenyl substituent were the most active Substitution of a halogen or nitro group in the *para* position of the phenyl group was found to enhance activity Substitution of an alkyl group in the 6 position of the pyrimidine also increased activity and in the case of 5 *p*-chlorophenyl derivatives a peak of activity was reached with the 6-ethyl compound (pyrimethamine) which proved 60 times as active as proguanil against *P gallinaceum and 200 times as active against P berghei*

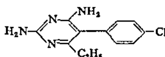
The active form of proguanil has been shown to be a metabolite which bears a striking resemblance to pyrimethamine What was originally proposed as a purely formal analogy is now, therefore, to be regarded as

a real structural analogy It is not surprising to find that the two compounds resemble one another closely in their antimalarial properties There is also evidence that pyrimethamine itself may give rise to an active metabolite

Graphic formulae



metabolite of proguanil

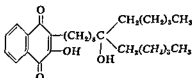


pyrimethamine

Naphthoquinones

Hydrolapachol and two other quinones have been found to possess some antimalarial activity and this has led to the synthesis of a number of other naphthoquinone derivatives Although some members of the group have shown considerable activity against avian plasmodia their effect in human malaria has been generally disappointing presumably because they undergo rapid degradation in the human body One of them, however, has been shown to have considerable resistance to metabolic deactivation, namely, Lapinone (M 2350), which has a hydroxylated C_{19} side chain It has been claimed that this drug has definite suppressive activity against vivax malaria, but this finding needs confirmation

Graphic formula



Lapinone

Organometallic compounds

... certain metallic
... nber of arsenical
... ıne (Salvarsan),
neoarsphenamine (Neosalvarsan), Mapharsen, acetarsol (Stovarsol), and carbarsone—but although arrested development of the parasites and relief

of symptoms have been recorded in vivax infections, there has been no consistent diminution in the relapse-rate Preparations of mercury, antimony, and bismuth have also been used for malaria with little success

A bismuth compound—sodium bismuth thioglycollate, known as Thio Bismol—has been found useful for limiting vivax and malariae infections in the treatment of neurosyphilis by malaria therapy It has an inhibitory action on the half and three quarter grown forms of the parasite and is used in vivax malaria for converting a quotidian type of fever into a tertian by destroying all except one generation of parasites Neoarsphenamine has been used similarly in the Netherlands

Antibiotics

Many antibiotics have been tested for antimalarial activity Some action was shown by certain members of the group—for example, Chloromycetin, Aureomycin, Terramycin, and Fumagillin—but in no case have the results indicated that the drug would prove of practical value in the treatment or prophylaxis of malaria

Miscellaneous

A number of amino alcohols derived from phenanthrene and naphthalene have been reported as showing antimalarial activity One of the phenanthrene derivatives (SN 1796) has been tested against human malaria, but the response was poor

Isolation of the active metabolite of proguanil has recently stimulated researches on substituted triazine derivatives and some of the compounds have been found more active than proguanil against experimental infections

In the field of aminocresols and orthocresols, a compound designated SN 6771 has been found to display some activity against human malaria

A number of pantothenic acid derivatives, thiocarbamates, diamidines, dicoumarins, dibenzamidines, hormones, vitamins and their analogues, sulfabiguanides, guanidines, thio derivatives, cinnolines, benzoacridines, and pyridoacridines have been tested, but in no case has any compound been discovered which could compete with the established antimalarial drugs

The Biological Approach

Life cycle of the malaria parasite

More than 50 years have passed since the mode of transmission of malaria was proved and the existence of an asexual phase in man and a sexual phase in the mosquito was demonstrated The latter was followed

out in full as early as 1898, but for many years one question regarding the former remained unanswered What happens to the parasite during the period between the injection of the sporozoites into the body and the first demonstrable appearance of asexual forms in the peripheral blood?

Schaudinn,[22] in 1902, reported that he had actually seen a sporozoite penetrate a red blood-cell, and this finding was at first generally accepted But as the years went by and no one was able to repeat this observation, despite the most intensive search, it gradually became evident that Schaudinn had been mistaken, and that the parasite must undergo another phase of development in the body during the prepatent period, as indeed had been suspected by Grassi as early as 1900

Raffaele,[21] who described unpigmented parasites in avian malaria in 1934, was the first to recognize that these forms represented a definite phase of development in the tissues as distinct from that occurring in the blood James & Tate,[17] in 1937, described the exoerythrocytic schizogony of *P gallinaceum* in the brain capillaries of the fowl, but the mystery of what happens during the period immediately after infection remained for a while unsolved

In 1940, however, Shortt and his colleagues[30] in India and Mudrow[20] in Germany independently observed pre erythrocytic forms of avian malaria during the prepatent period This work was amplified in the United States of America by Huff & Coulston[15] who, in 1944, described in detail the complete development of the pre erythrocytic stages of *P gallinaceum*

Between 1943 and 1945, Fairley and his co workers[7] in Australia carried out some highly significant studies on human malaria by which it was shown that after infection by mosquito bites the sporozoites circulate in the blood for about half an hour, after which they disappear This was proved by inoculating large quantities of blood into volunteers in whom malaria was produced if the blood was drawn from the donor within half an hour of infection Subsequently the blood of the donor was innocuous for six days after inoculation with *P falciparum* and for eight days after that with *P vivax*

At this time Shortt and Garnham in England had just begun a series of researches on mammalian malaria that were destined to achieve far-reaching results In 1948, after massive infection by the bites of heavily infected mosquitos, which were afterwards ground up and injected parenterally into a rhesus monkey, pre-erythrocytic forms of *P cynomolgi* were observed in a section of liver removed seven days later[29]

Subsequently, less mature stages of the parasite were found in the liver of other monkeys similarly infected, the earliest to date being in sections excised on the second day[28] It has also been proved that in monkey

malaria exoerythrocytic parasites can persist in the liver after blood infection has been established These forms are thought to be responsible for the phenomenon of late relapse in cynomolgi and vivax malaria As such relapses are not encountered in falciparum infections, it is believed that such a phase does not occur in this type of malaria

The demonstration of tissue forms of *P cynomolgi* in the monkey made it practically certain that a similar phase exists in human malaria, and this was soon established for both *P vivax* and *P falciparum* This work was carried out by Shortt and his team in London, in collaboration with the staff of Horton Malaria Laboratory [25, 26] In December 1953, Garnham and his co workers succeeded in demonstrating pre-erythrocytic forms of *P ovale* in the human liver [11] Two years earlier, Garnham [10] had demonstrated in the liver of a monkey pre erythrocytic forms of *P inui* which closely resembles *P malariae* in all essential features The existence of a pre erythrocytic phase of *P falciparum* has been confirmed by Jeffery and his colleagues [19] in the United States of America

The life-cycle of the malaria parasite may be summarized as follows When an infective mosquito bites a new host, sporozoites are inoculated into the blood stream There they circulate for about half an hour, after which they disappear It is presumed that many of them are arrested in the liver although the earliest stage of development in that organ has not yet been observed As stated above, however, pre-erythrocytic forms of *P cynomolgi* have been demonstrated as early as the second day after infection The tissue schizont, as the parasite is now called, increases in size and divides to form thousands of minute merozoites The cell envelope ruptures, setting free the merozoites into the surrounding tissues Many of these probably attach themselves to red cells in the liver sinusoids, but it is believed that, except in falciparum malaria, some penetrate other liver cells and either remain dormant or repeat the cycle of schizogony These are the forms to which late relapses in vivax malaria have been attributed

The young merozoites which enter the blood stream are now called trophozoites It is generally believed that the parasite actually penetrates the red cell, but some observers hold that it remains on the outer surface The trophozoites increase in size and become schizonts These ultimately rupture, discharging merozoites, which enter other red cells and repeat the process of schizogony After a while certain merozoites are produced which become sexually differentiated as male and female gametocytes Should a mosquito bite the host at this time the sexual forms are taken up and conjugate in the insect s stomach to form a zygote This lengthens to become an ookinete or vermicule, which penetrates the stomach wall and comes to rest on the outer surface, where it is known as an oocyst The cyst grows and divides into thousands of elongated

bodies called sporozoites When the cyst ruptures, many of the sporozoites find their way into the salivary glands, whence they are injected into a new host when the mosquito next takes a blood meal

Drug action in relation to different stages of the life cycle

In theory, a drug may act on the malaria parasite in any of the following ways (1) against the sporozoites when they first enter the human body, (2) against the primary tissue or pre erythrocytic forms of the parasite, (3) against the asexual parasites in their erythrocytic phase, (4) against the sexual parasites in their erythrocytic phase, (5) against the late exoerythrocytic or secondary tissue phase, to which the phenomena of latency and late relapse in vivax and possibly in quartan malaria have been attributed, and (6) against the sporogonic forms in the mosquito phase of the life-cycle

T[illegible] belong
are
acri[illegible]
quine), (*d*) the 8 aminoquinolines (pamaquine, primaquine), (*e*) the biguanides (proguanil), and (*f*) the diaminopyrimidines (pyrimethamine)

No drug yet tested has any demonstrable effect on the sporozoite stage of the malaria parasite The cinchona alkaloids, aminoacridines, 4-amino-[illegible]
sites, but they have a powerful destructive action on the gametocytes of all species They also act on the secondary exoerythrocytic forms of *P vivax*, and it is in this respect that they have their greatest value They have an inhibitory effect on the pre erythrocytic forms of both *P falciparum* and *P vivax* but cannot be used for this purpose without risk of toxicity

The biguanides and the diaminopyrimidines are the only drugs which can be used with safety against the pre erythrocytic forms, and so far as is known they are fully effective only in falciparum infections They have no apparent action on the sexual forms of *P falciparum* in the peripheral blood, but both render these incapable of completing their development in the mosquito

Antimalarial drugs may thus be placed in groups according to the stage of the life cycle on which they act, viz

(1) *Drugs acting on pre erythrocytic forms* (primary tissue schizontocides, causal prophylactics) For practical purposes, only proguanil and pyrimethamine come under this heading

(2) *Drugs acting on asexual erythrocytic forms* (blood schizontocides *) While most antimalarial drugs have some action on these forms, the only ones which are of practical value for treatment of the clinical attack are chloroquine and related 4-aminoquinolines, mepacrine, and quinine. These drugs are effective suppressants of all species of human malaria parasites, and will effect radical cure in most cases of falciparum infection Proguanil and pyrimethamine are also effective suppressants, but are not sufficiently rapid in action for treatment of the clinical attack in a non immune subject

(3) *Drugs acting on late exoerythrocytic forms* (secondary tissue schizontocides; anti-relapse drugs) The only compounds in this category known to be effective are the 8-aminoquinolines (pamaquine, primaquine)

(4) *Drugs acting on the sexual forms* (gametocytocides) Pamaquine and probably other 8-aminoquinolines have a powerful destructive action [illegible] the peripheral blood within a few days of treatment with these drugs.

(5) *Drugs acting on the sporogonic forms in the mosquito* (sporontocides) Proguanil and pyrimethamine come under this heading

Pharmacological considerations

An enormous volume of research has been devoted to studies of the pharmacology of antimalarial drugs, but there are still many gaps left in knowledge of the subject, even in respect of the cinchona alkaloids For the effective treatment of the clinical attack, an adequate concentration of the drug in the red blood-cells, where the parasites reside, is essential The concentration attained in these cells by different drugs, however, shows wide variations That of quinine may be as low as one-eighth of the concentration in the plasma The low cell concentration attained by quinine as compared with other schizontocidal drugs is no doubt a reason why so much higher doses are required to produce the necessary effect

Factors which affect the attainment and maintenance of an adequate drug concentration in the red cells include the rate of absorption of the drug from the alimentary canal, competition for the drug between the red cells and various body constituents, such as the plasma proteins and tissue cells, and the rate at which the body degrades and excretes it

Mepacrine and the 4-aminoquinolines are rapidly absorbed and soon become localized in the tissues; degradation and excretion are slow and

* This term has been suggested to distinguish these drugs from those acting on tissue schizonts, but they are still commonly designated schizontocides without qualification

consequently these drugs persist in the body for long periods It is therefore necessary to administer a high initial, or loading dose, the red-cell con centration being kept at the required level thereafter by a lower mainten ance dosage It is interesting to note that the principle of giving a high loading dose of mepacrine, put forward by Shannon and his colleagues[24] in 1944, to enhance the therapeutic effectiveness of the drug, has found general acceptance among clinicians, the principle applies equally well in the use of chloroquine and other 4-aminoquinolines

Quinine and the 8 aminoquinolines are rapidly absorbed, but plasma concentrations fall very rapidly in both instances It is therefore necessary to administer doses as high as possible and at frequent intervals, rather than a high loading dose followed by a lower *maintenance dose*

Proguanil and pyrimethamine are active in very low concentrations, so [illegible]

It is recognized, however, that there are other factors besides blood concentration to be taken into consideration There is evidence, for instance, that proguanil and pamaquine, and probably also pyrimethamine, are not themselves active agents, but owe their efficacy mainly to a trans formation within the body into active metabolites Further details regard ing the pharmacological action of individual drugs are given in chapter 3

The varying response of different strains of the parasite

Infections produced by strains of the same species of malaria parasite from different geographical areas may show wide variations in patho genicity, ability to develop in the mosquito host, relapse pattern, and immunological properties It is not surprising therefore, that differences in their response to the action of a particular drug are sometimes encountered More than 30 years ago, James and his colleagues observed that the amount of quinine required to control infections with Italian strains of *P falciparum* was several times as great as that needed for the management of infections with a strain of the same species of parasite from India In recent years, a number of similar instances have been recorded Infections with a New Guinea strain of *P falciparum* were successfully treated with proguanil by Fairley and his colleagues, whereas the same drug proved ineffective for radical cure of an infection with a strain of the same species of parasite imported to England from West Africa In prophylaxis, however, the drug proved equally effective against either strain Again, the Chesson strain of *P vivax* from New Guinea was found to be more refractory to both quinine and mepacrine than the McCoy strain from the southern United States of America

The Chesson strain, which is characterized by a series of relapses occurring at short intervals following the primary attack, was also found by Coatney and his colleagues to be much more refractory to anti-relapse treatment with primaquine than the long term relapsing St Elizabeth strain originally encountered in the United States of America

The relapse rate in vivax malaria is closely related to the manner in which the primary attack is treated Thus, with the Madagascar strain used in England for malaria therapy of neurosyphilis, if the patient is allowed to have a succession of 12 to 14 febrile paroxysms before treatment is begun, the relapse rate is about 50%, whereas, if an efficient blood schizontocide is administered early in the attack, the rate may reach 90% or even higher *

The immunity factor

Many persons of the Negro race and occasional individuals of other races are highly refractory to infection with vivax malaria This is an example of *natural immunity*, as distinct from *acquired immunity*, which is the result of past or present infection

Tolerance is an acquired immunity contingent on and conditioned by the continued presence of the parasite in the host A host with tolerance exhibits less reaction to a given quantum of infection, whereas one with natural immunity has an increased ability to limit the quantum of infection developed *Premunition* is almost synonymous with tolerance, but has a greater connotation of immunity to superinfection with the same parasite

In malaria the immunity response is directed primarily against the asexual parasites in the blood, the tissue forms in the liver being completely protected from the cellulo humoral immunity response An acquired immunity is most effective against infection with the same strain of parasite, but it may operate against heterologous strains to some degree

The efficacy of an antimalarial drug cannot be properly assessed until it has been subjected to carefully controlled experimentation on subjects who are completely non immune

Synergism

There are many examples in chemotherapy where the action of a particular drug is enhanced or reinforced by the concurrent administration of another Sinton and his colleagues in India concluded that a combination of quinine with pamaquine was more effective for radical cure of vivax

* It is not suggested however that specific treatment of an overt malarial attack should be delayed on this account

infections than the action of either drug given separately As the result of these findings it has generally been accepted that quinine has a synergistic action on the 8 aminoquinolines or on their active derivatives enabling them to destroy the late exoerythrocytic parasites more effectively and so prevent relapses Recent observations in the United States of America on avian and simian malaria have, however, thrown some doubt on this theory Coatney and his colleagues were unable to demonstrate synergism between quinine and the 8 aminoquinolines against gallinaceum infections, and Schmidt has been equally unsuccessful in experiments with *P cyno-molgi*, whose behaviour resembles that of the late relapsing strain of *P vivax* in so many respects These findings suggest that the two classes [illegible] the 8 [illegible] on the late tissue

of Korean vivax malaria among United States military personnel by the routine administration of primaquine alone

Greenberg and his co workers[13] have shown that proguanil and sulfa diazine potentiate each other s action against *P gallinaceum*, and have demonstrated a synergism between proguanil and *p* aminobenzoic-acid antagonists which themselves act against gallinaceum infections

Effect of drugs on plasmodium metabolism

The first researches undertaken on the subject of the effect of drugs on plasmodium metabolism were those of Christophers & Fulton,[2] who published results of their studies on the respiratory metabolism of *P knowlesi* in 1938 Intensive investigations on the biochemistry of erythrocytic stages of malaria parasites were continued during the second World War, par ticularly in the United States of America The metabolic activities of the parasites were found to resemble closely those of other organisms previously studied

It was known that quinine has the property of inhibiting certain enzymes, and it seemed possible that the therapeutic effect of antimalarial drugs might be measu ed by their power to inhibit the respiration of malaria parasites The quantitative effect of various compounds on the oxygen uptake of malaria parasites was therefore investigated and it was found that the inhibitory action was in some degree parallel with the therapeutic effect Except in the case of certain naphthoquinones, however, the corre lation between inhibition of respiration of a malaria parasite and thera-peutic efficiency of a drug was poor

A number of other researches have been planned with the object of discovering some vulnerable link in the metabolic chain and in the growth

requirements of malaria parasites which might provide a clue to the synthesis of more effective drugs

From studies on the respiration and carbohydrate metabolism of malaria parasites it is possible to indicate certain points where these processes are deranged by antimalarial drugs There are also indications that certain vitamins, such as *p*-aminobenzoic acid, pantothenic acid, and folic acid, if deficient or in excess, may influence antimalarial action Little is as yet known of the nitrogen requirements or nitrogen metabolism of malaria parasites, but it seems probable that while the parasite relies on the red cell for its protein metabolism, protein hydrolysis is linked up with oxidative processes Further studies are necessary before the possible action of antimalarial drugs on protein metabolism can be explained on a satisfactory basis

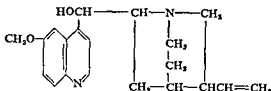
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CHAPTER 3

INDIVIDUAL COMPOUNDS IN COMMON USE

Quinine *

Formula



quinine 6 methoxy (5 vinyl 2-quinuclidyl)-4-quinol nemethanol

Activity in human malaria

(*a*) Sporozoites
(*b*) Primary exoerythrocytic forms } Inactive Quinine is hence useless for *causal prophylaxis*

(*c*) Asexual erythrocytic forms A highly active blood schizontocide in all forms of human malaria, and hence an efficient drug for clinical cure With prolonged administration *radical cure* is often possible in falciparum infection, but seldom in vivax infection For *suppression* and *suppressive cure* quinine is less efficient than mepacrine or the better known 4 amino quinolines

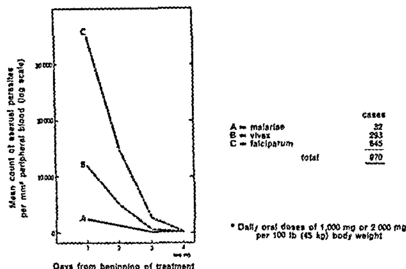
(*d*) Gametocytes Quinine has little gametocytocidal activity in fal ciparum malaria but is an effective gametocytocide in vivax and quartan malaria , for general *gametocytocidal prophylaxis* it is a poor drug

(*e*) Secondary exoerythrocytic forms Inactive Quinine is thus a poor drug for *radical cure* in vivax malaria when used alone , when com bined, however, with certain of the 8 aminoquinolines a high cure rate is possible in vivax infection

(*f*) General The value of quinine in the treatment of malaria is attested by long experience Safe to use, consistent in action on the schizo- gonic blood forms, it may be used with confidence for the relief of symp- toms in acute malaria , and, indeed, for the immediate treatment of severe

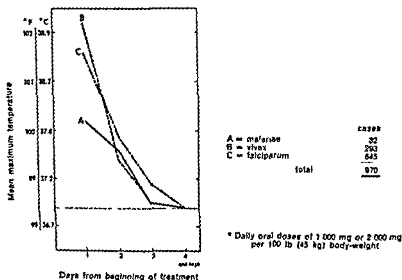
* See Selected bibliography No 33 39 (page 106)

FIG 1 EFFECT ON ASEXUAL PARASITAEMIA IN ACUTE MALARIA OF THERAPEUTIC DOSES OF QUININE DIHYDROCHLORIDE *



Unpublished data from Institute for Medical Research Federation of Malaya 1933-41

FIG 2 EFFECT ON FEVER IN ACUTE MALARIA OF THERAPEUTIC DOSES OF QUININE DIHYDROCHLORIDE *



Unpublished data from Institute for Medical Research Federation of Malaya 1933-41

falciparum infection, some authorities believe that quinine is unsurpassed by any of the new synthetic compounds Its value as an adjuvant to the 8 aminoquinolines for the radical cure of vivax malaria is discussed in chapter 5 (page 82)

Toxicity

Serious toxic effects from the clinical use of quinine are very rare, but the drug has its own characteristic side effects Giddiness, deafness, ringing in the ears, tremors, and blurred vision may occur during the first few days of administration, particularly when the plasma level exceeds 12 mg per litre These symptoms, collectively known as cinchonism are seldom severe enough to interfere with treatment, they subside quickly when administration ceases and are never of serious import Given intra venously, quinine lowers the blood pressure Fatal collapse may occur as a result of intravenous injections administered too quickly in very severe infection

Idiosyncrasy to quinine occurs, but is rare Urticarial or erythematous rashes with intense itching, subcutaneous or submucous haemorrhages, oedema of the eyelids, mucous membranes, or lungs, and even collapse, have been known to follow a single dose Excessive dosage may cause temporary blindness or deafness, possibly with permanent impairment of sight or hearing Recovery from a single oral dose of 10 000 mg (150 grains) and death from a single dose of 16,000 mg (240 grains) have been reported

Contraindications

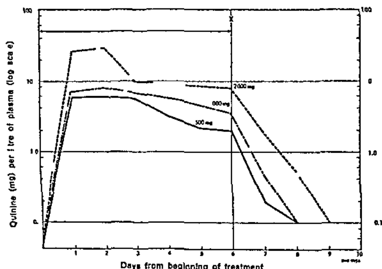
There are few contraindications to the use of quinine in the treatment of malaria Patients with an idiosyncrasy to quinine must obviously be treated with some other drug, and a history or threat of blackwater fever is a clear indication for withholding quinine in favour of one of the synthetic compounds The controversial question of quinine in pregnancy has lost its urgency with the modern developments in therapy, untreated malaria is more likely to induce abortion than is quinine, but most physicians will play for safety by using some alternative drug

Absorption, elimination, plasma concentration

Quinine passes through the stomach unchanged and is quickly and almost completely absorbed from the upper intestinal tract to circulate as a base The rate of absorption is not greatly affected by the route of administration, and the drug appears in the urine in an hour or less whether

given by the mouth or by intramuscular or intravenous injection Quinine is quickly destroyed by the tissues or excreted unchanged in the urine, and little remains in the body 48 hours after the last dose Peak concentrations in the plasma are reached from one to three hours after administration by mouth, the amount in the red cells being about one fifth of that in the plasma A mean plasma concentration of 2 5 mg per litre is

FIG 3 CONCENTRATION OF QUININE (GROUP MEANS) IN PLASMA DURING TREATMENT WITH 500 mg 1 000 mg AND 2 000 mg OF QUININE SULFATE DAILY FOR SIX DAYS



X = end of treatment

After Coatney et al [16]

probably necessary to reduce parasitaemia in acute vivax malaria, and 5 mg per l [illegible]

species the effective plasma level may depend on the strain of parasite

Dosage and route of administration

See chapter 5

Test for detection in body fluids

Quinine may be detected in the urine by Mayer's test

Mayer's reagent

Mercuric chloride	6,800 mg
Potassium iodide	24,900 mg
Distilled water	500 *ml*

Procedure

(*a*) Add clear urine to each of two test tubes (cloudy urine should be shaken with kieselguhr and filtered)

(*b*) To one tube add a few drops of acetic acid

(*c*) To both tubes add a few drops of the reagent

Interpretation

(*a*) If both tubes remain clear, the test is negative

(*b*) If both tubes show turbidity, the presence of quinine is probable Confirm by demonstrating the disappearance of turbidity on boiling the acidified urine in tube 2 Should the urine remain turbid the presence of albumin is probable Filter hot to remove the albumin quinine precipitates as the filtrate cools

(*c*) If the acid tube alone shows turbidity, the presence of quinine, albumin, or both may be inferred To identify quinine, boil and filter hot, as in (*b*) Precipitates due to quinine and albumin appear almost immediately Sometimes turbidity develops slowly in the acid tube, when the presence both of quinine and albumin can be excluded Precipitates which appear late may be ignored for the purpose of the test

Cinchona mixtures

Mixtures of cinchona alkaloids have one advantage over quinine they are cheaper Their activity in the treatment of malaria is essentially the same they cannot be used for injection and they are rather more likely to cause nausea or vomiting According to the definition of the Malaria Commission of the League of Nations, totaquina (totaquine) is a mixture containing not less than 70% of crystallizable cinchona alkaloid, of which not less than 15% is quinine, nor should it contain more than 20% of amorphous alkaloids It should not contain more than 5% of water, and the mineral ash-content should not exceed 5%, preferably 3%

Salts in common use

Sulfate, bisulfate, hydrochloride, and dihydrochloride, prescribed either in solution or in tablets or capsules

Physical data regarding salts

See Annex 3

Primaquine and Other 8-aminoquinolines *

Formulae



pamaquine 8-(4-diethylamino 1 methylbutylamino)-6-methoxyquinoline



primaquine 8-(4-amino 1 methyl butylamino) 6-methoxyquinoline

Activity in human malaria

(*a*) Sporozoites Probably inactive

(*b*) Primary exoerythrocytic forms Active against these forms of *P vivax* and *P falciparum*, particularly the latter Activity against these forms of *P malariae* is not known

(*c*) Asexual blood forms Active against the asexual blood forms of *P vivax* and *P falciparum*, but only at a dosage dangerously high for routine use

(*d*) Gametocytes *Highly active against the gametocytes* of all species of human malaria parasite

(*e*) Secondary exoerythrocytic forms Highly active *Radical cure* of vivax malaria is usually produced whether the drug is administered during a relapse or during latency Data on similar presumed stages of quartan malaria are not available

(*f*) General The discovery in pamaquine of a drug which could act

* See Selected bibliography No 40-53 (page 107)

asexual blood parasites, like that of the other 8-aminoquinolines, is effective only at dangerously high dosage has, however, precluded its use for treatment of the acute attack, though it has been used extensively for the prevention of relapse in vivax malaria, for which until recently it was the only drug available It seems likely that primaquine, with its lower toxicity and greater effectiveness against fixed tissue stages of the parasite, will eventually supersede pamaquine for the radical cure of relapsing malaria Studies are now in progress to investigate its effectiveness for prophylactic suppression

Toxicity

At the recommended dosage, no symptoms of toxicity are likely When include anorexia, nausea, id cramps, the passage of chest pain, and weakness In addition, there may be striking effects on the formed elements of the blood and the bone marrow, marked by leukopenia, anaemia, methaemoglobinaemia, and suppression of myeloid activity, with lesser effects on the heart and circulation These manifestations disappear when the drug is withdrawn The tendency for haemolytic reactions is increased in all the dark-skinned races

Contraindications

Because the tendency for methaemoglobinaemia and granulocytic neutropenia, and probably for acute haemolytic anaemia, is potentiated by mepacrine, none of the 8 aminoquinolines should be administered concurrently with, or immediately following, treatment with mepacrine

Absorption, elimination

All the 8-aminoquinolines are rapidly absorbed, elimination is accomplished entirely within 24 hours through metabolic conversions and excretion of the degradation products in the urine, only a very small amount is fixed in the tissues

Dosage and route of administration

See chapter 5

Tests for detection in body fluids

Because of the rapidity of elimination and of the low dosages needed to effect cure, tests for plasma concentration of the 8-aminoquinolines are neither needed nor recommended

Salts in common use

Primaquine diphosphate, pamaquine naphthoate and monohydrochloride

Physical data regarding salts

See Annex 3

Synonyms

See Annex 4

Mepacrine *

Formula



mepacrine 6-chloro 2 methoxy 9 (4-diethylamino-1 methylbutylamino)acridine

Activity in human malaria

(*a*) Sporozoites Probably inactive

(*b*) Primary exoerythrocytic forms Inactive against these forms of all species of malaria parasite

(*c*) Asexual blood forms Highly active against the asexual blood forms of all species Will produce *clinical cure* of all types of human malaria and *radical cure* of falciparum infection Mepacrine is an excellent *suppressive* agent against all species of human malaria parasite and in falciparum infection it can effect *suppressive cure* Morphological changes, marked by a distinctive clumping of the pigment, are characteristic of its action

(*d*) Gametocytes Mepacrine acts as a gametocytocidal agent against *P vivax* and *P malariae*, it is ineffective against the gametocytes of *P falciparum*

(*e*) Secondary exoerythrocytic forms Inactive Mepacrine will not effect *radical* or *suppressive cure* of vivax malaria The effect on similar presumed stages of quartan malaria is unknown

* See Selected bibliography, No 54 71 (a) (page 109)

(*f*) General Mepacrine is superior to quinine in that (1) it has greater antimalarial activity against asexual blood parasites both as a suppressant and as a therapeutic agent, particularly against certain strains of *P falciparum*, (2) its use is attended by a lower incidence of blackwater fever, (3) it is a synthetic product and therefore supply is not affected by vicissitudes of nature or by geographical location Even with these advantages the drug has certain limitations (i) it dyes the skin and conjunctivae yellow and occasionally causes alarming, though transient, mental disturbances (see below), (ii) it must be given daily, or not less than twice weekly, for complete suppression of all types of malaria, (iii) adequate management of acute malarial attacks in non immune subjects may require seven days of drug administration

Toxicity

When administered initially at the recommended dosage, gastrointestinal distress may appear in the form of abdominal cramps, nausea, vomiting, and diarrhoea, but these symptoms disappear with continued administration of the drug Mental symptoms varying from pronounced depression to extreme excitement or even mania may occasionally occur, but these disappear when the drug is withdrawn Under humid tropical conditions cutaneous lesions (atypical lichen planus) may develop into a generalized exfoliating dermatitis Aplastic anaemia has also been attributed to prolonged ingestion of mepacrine

Contraindications

Apart from individual idiosyncrasy, syphilis affecting the central nervous system is the only contraindication to the use of mepacrine in the treatment of malaria [71a] Convulsive seizures have been recorded in such patients following its administration, and it is advisable, therefore, to use some other drug for the management of malaria in such cases

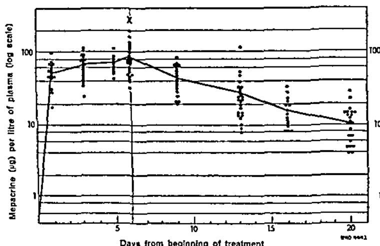
Absorption, elimination, plasma concentration

Absorption of the drug is rapid, elimination is slow, due to its pronounced affinity for the organs and tissues, where the concentration may reach several hundred times that found in the plasma Only about 10% or less is eliminated in the urine daily, with the result that from three to four weeks are required for concentrations to drop below non effective levels Peak concentrations of 50 60 µg per litre in plasma are attained
When doses
plasma

Dosage and route of administration

See chapter 5

FIG 4 INDIVIDUAL CONCENTRATIONS AND GROUP MEANS OF MEPACRINE IN PLASMA DURING AND FOLLOWING 6-DAY THERAPEUTIC COURSES *



X = end of treatment

——— mean concentration

• ... individual concentration

* 200 mg of mepacrine hydrochloride 4 times daily the first day followed by 100 mg of mepacrine hydrochloride 4 times daily for 5 days

After Cooper et al [57]

Tests for estimation in body fluids

(1) For estimation of mepacrine in body fluids, a single extraction procedure has been developed by Brodie et al [56]

Reagents

(*a*) 0 1 N NaOH

(*b*) Heptane a technical grade is purified by successive washings with 1 N NaOH, 1 N HCl, and water

(*c*) *Iso*-amyl alcohol, reagent grade

(*d*) Trichloroacetic acid solution 2,500 mg of the acid are dissolved in 100 ml of ethylene dichloride

Procedure

(a) Add 1 5 ml of biological fluid and an equal volume of 0 1 N NaOH to 15 ml of heptane in a 60-ml glass stoppered bottle

(b) Shake for 30 minutes Allow the phases to separate, centri fuging if necessary

(c) Add 0 5 ml of *iso* amyl alcohol and mix with the heptane phase so as not to disturb the aqueous phase

(d) *Transfer 10 ml of the heptane phase material to a fluorometer* tube containing 1 ml of trichloroacetic acid solution A blank of the heptane, *iso* amyl alcohol and the trichloroacetic acid solution is used *for the setting of the fluorometer If a reagent blank—namely, with* water substituted for plasma or urine—is run, the reading should be the same as the blank set up with pure chemicals

Standards are prepared by extracting known amounts of mepacrine in the same manner as the biological sample The computation of mepacrine concentration is by direct proportion

(2) A modification of the test, devised by Wats & Ghosh,[71] has been found useful in Malaya

(a) To 10 ml of urine in a test tube add 1 ml of saturated solution of potassium carbonate

(b) To the alkalinized urine add 0 25 ml of amyl alcohol

(c) *Thoroughly shake and put aside for a few minutes to allow* the alcohol to separate

(d) Examine by ultra violet light for yellow fluorescence in the alcohol layer

The alcohol layer contains most of the mepacrine When examined by ultra violet light, the extracted mepacrine fluoresces a vivid yellow The test is extremely sensitive and reveals the presence of mepacrine in a dilution approaching one part in two and a half million

Salts in common use

Dihydrochloride dihydrate, methane sulfonate

Physical data regarding salts

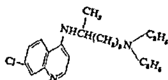
See Annex 3

Synonyms

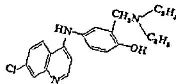
See Annex 4

Formulae

Chloroquine and Other 4-aminoquinolines *



chloroquine 7-chloro-4-(4 diethylamino-1 methylbutylamino)quinoline



amodiaquine 7-chloro-4-(3-diethylamino-methyl-4-hydroxyanilino)quinoline

Activity in human malaria

(*a*) Sporozoites Probably inactive

(*b*) Primary exoerythrocytic forms Inactive in all types of malaria

(*c*) Asexual blood forms Chloroquine and amodiaquine are highly effective against the asexual blood forms of all species of malaria parasite They will produce *clinical cure* of all types of human malaria and *radical cure* of falciparum infection They are excellent *suppressive* agents against all species, such administration continued for from three to four weeks, results in *suppressive cure* of falciparum malaria Morphological changes, marked by distinctive clumping of pigment, are characteristic of their action

(*d*) Gametocytes Chloroquine and amodiaquine act as gametocytocidal agents against *P vivax* and *P malariae*, they are ineffective against the gametocytes of *P falciparum*

(*e*) Secondary exoerythrocytic parasites Inactive They will not produce *radical* or *suppressive cure* of vivax malaria The effect on similar presumed stages of quartan malaria is unknown

(*f*) General Chloroquine and amodiaquine are superior to mepacrine in that (1) they have greater activity as suppressive and therapeutic agents, fever is usually absent after 24 hours with elimination of patent parasitaemia in from 48 to 72 hours, (2) less frequent administration is required for effective results, (3) periods of latency are longer, (4) there is less tissue reaction following intramuscular administration, (5) they do not stain the skin or conjuctivae

Sontoquine and other 4 aminoquinolines hitherto tested have proved less active than chloroquine or amodiaquine as regards antimalarial properties

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* See Selected bibliography, No 72-88 (page 109)

Toxicity

Toxicity is extremely low at doses ordinarily employed for therapy or suppression and although headache, pruritus, and blurring of vision have been reported following therapeutic doses, these symptoms usually disappear shortly after administration has been discontinued

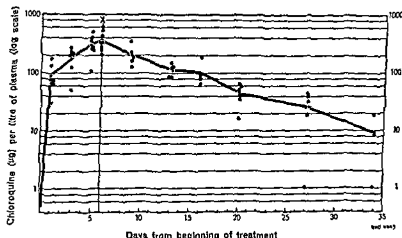
Contraindications

No contraindications have been reported to date

Absorption, elimination, plasma concentration

Absorption from the gastro intestinal tract is rapid and almost complete These drugs are extensively localized in the tissues, from where they are metabolized and excreted slowly On an equal dose basis, concentrations of chloroquine in the plasma are from 10 to 20 times higher and persist longer than is the case with mepacrine, concentrations of chloroquine in the plasma tend to be higher than with other 4 aminoquinolines Under accepted regimens of therapy employing loading doses, effective chloroquine concentrations are reached within from two to three hours When the drug is given intramuscularly, therapeutically effective plasma chloroquine concentrations are reached in less than 15 minutes

FIG 5 INDIVIDUAL CONCENTRATIONS AND GROUP MEANS OF CHLOROQUINE IN PLASMA DURING AND FOLLOWING 6-DAY THERAPEUTIC COURSES *



X = end of treatment
—— mean concentration
.... individual concentration

* 200 mg of chloroquine (base) 4 times daily the first day followed by 100 mg of chloroquine (base) 4 times daily for 5 days

After Coatney et al [11]

Dosage and route of administration

See chapter 5

Test for estimation in body fluids

A double extraction procedure for the estimation of chloroquine in body fluids has been worked out by Brodie et al [58]

Reagents

(*a*) Standard solution of chloroquine, 100 mg per litre 161 mg of the diphosphate salt are dissolved in 1 litre of 0 1 N HCl This solution is stable when stored in the refrigerator Working standards are prepared daily by dilution with 0 1 N HCl

(*b*) 0 1 N NaOH

(*c*) Heptane a technical grade of heptane is purified by successive washings with 1 N NaOH, 1 N HCl, and water

(*d*) Absolute ethanol

(*e*) 0 1 N HCl

(*f*) 0 5 N NaOH 1 ml should be neutralized by 5 ml of the above 0 1 N HCl

(*g*) Buffer reagent, pH 9 5 5 volumes of 0 6 M boric acid in 0 6 M KCl are added to 3 2 volumes of 0 6 N NaOH When diluted as described in the procedure and after the addition of the cysteine reagent, the resulting pH should be 9 4-9 6 This pH should be checked by direct measurement

(*h*) 5% cysteine reagent 1 000 mg of cysteine hydrochloride is dissolved in 20 ml of water This solution is neutralized by the addition of 0 8 ml of 10 N NaOH This reagent should be made fresh daily and neutralized just before use

Procedure

(*a*) Add 1 10 ml of biological sample (containing up to 1 μg of chloroquine) and an equal volume of 0 1 N NaOH to 30 ml heptane in a 60-ml glass stoppered bottle

(*b*) Shake for 30 minutes Allow the phases to separate, centrifuging if necessary

(*c*) Add 8 drops of ethanol and mix with the heptane phase so as not to disturb the aqueous phase

(*d*) Transfer the heptane to a 125-ml glass stoppered bottle, add about twice the volume of 0 1 N NaOH and shake for 5 minutes

(*e*) After settling add 8 drops of ethanol to the heptane and mix as before Remove the aqueous phase by aspiration

(*f*) Repeat the washing with 0 1 N NaOH, add 5 drops of ethanol, and transfer 20 ml of the heptane to a 60-ml glass stoppered bottle containing 6 ml of 0 1 N HCl

(*g*) Shake for 3 minutes and then centrifuge for 2 minutes

(*h*) Transfer 5 ml of the acid phase to a fluorometer tube containing 1 0 ml of 0 5 N NaOH and 1 5 ml of buffer reagent Add 0 5 ml of cysteine reagent and mix

(*i*) A reagent blank, with water substituted for plasma or urine, is run through the same procedure

Standards are prepared by adding known amounts of the drug in 5 ml of 0 1 N HCl to 1 ml of 0 5 N NaOH and 1 5 ml of buffer in fluorometer tubes 0 5 ml of cysteine reagent is added to each tube A " dummy ", *consisting of acid, alkali, buffer, and cysteine reagent, is used for the* blank setting of the fluorometer After 30 minutes all tubes are irradiated with ultra-violet light, as described below

The intensity of fluorescence of the irradiated samples is determined in the Coleman photofluorometer, using Coleman B_1S and Coleman PC_1 filters The sensitivity of the instrument is set by quinine, since the irradiated standards may slowly lose their fluorescence on frequent exposure to the ultra-violet light of the fluorometer

Irradiation of the 4-aminoquinolines is effected in a simply constructed irradiator, using an H-4 mercury arc lamp as the light source The samples are placed in a circular rack surrounding the lamp so that they are equidistant from the lamp, and are irradiated for 3 hours A fan is used for keeping the temperature of the solutions below 35°C during irradiation

Salts in common use

Chloroquine diphosphate and dihydrochloride, amodiaquine dihydrochloride dihydrate

Physical data regarding salts

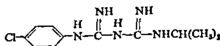
See Annex 3

Synonyms

See Annex 4

Proguanil *

Formula



proguanil N_1 *p*(-chlorophenyl) N_5-isopropyl biguanide

* See Selected bibliography, No 89 113 (page 110)

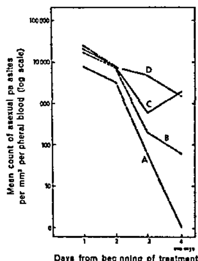
Actıvıty ın human malarıa

(*a*) Sporozoıtes Probably ınactıve

(*b*) Prımary exoerythrocytıc forms Proguanıl ıs hıghly actıve agaınst the prımary exoerythrocytıc forms of *P falcıparum* and has a fleetıng ınhıbıtory actıon on those of *P vıvax*, ıts actıon on the presumed prımary exoerythrocytıc forms of *P malariae* ıs unknown It ıs thus a powerful drug for *causal prophylaxıs* ın falcıparum malarıa

(*c*) Asexual blood forms Actıve agaınst the asexual blood forms of all specıes of human malarıa parasıte It wıll achıeve *clınıcal cure* ın all forms of malarıa, wıth *radıcal cure* ın most falcıparum ınfectıons, but the clınıcal response ıs slow, and ıts use for the treatment of an acute malarıal attack ıs not recommended It ıs a good *suppressıve* of all forms of malarıa, often wıth *suppressıve cure* ın falcıparum ınfectıon It appears to act by ınhıbıtıng nuclear dıvısıon

FIG 6 PARASITAEMIA IN 268 CASES OF ACUTE FALCIPARUM MALARIA TREATED IN MALAYA WITH PROGUANIL ILLUSTRATING A DEVELOPING RESISTANCE IN THE SCHIZOGONIC BLOOD FORMS



		cases
A =	proguanil single dose 100 mg (1947-8)	26
B =	" 250 mg or 300 mg (1948)	40
C =	250 mg or 300 mg (1949)	74
D =	" daily 300 mg (standard course) (1950-1)	128
	total	268

Data from Malarıa Research Dıvısıon Instıtute for Medıcal Research Federatıon of Malaya 1946-7

(*f*) Repeat the washing with 0 1 N NaOH, add 5 drops of ethanol, and transfer 20 ml of the heptane to a 60-ml glass-stoppered bottle *containing 6 ml of 0 1 N HCl*

(*g*) Shake for 3 minutes and then centrifuge for 2 minutes

(*h*) Transfer 5 ml of the acid phase to a fluorometer tube containing 1 0 ml of 0 5 N NaOH and 1 5 ml of buffer reagent Add 0 5 ml of cysteine reagent and mix

(*i*) A reagent blank, with water substituted for plasma or urine, is run through the same procedure

Standards are prepared by adding known amounts of the drug in 5 ml of 0 1 N HCl to 1 ml of 0 5 N NaOH and 1 5 ml of buffer in fluorometer tubes 0 5 ml of cysteine reagent is added to each tube A "dummy", consisting of acid, alkali, buffer, and cysteine reagent, is used for the blank setting of the fluorometer After 30 minutes all tubes are irradiated with ultra-violet light, as described below

The intensity of fluorescence of the irradiated samples is determined in the Coleman photofluorometer, using Coleman B_1S and Coleman PC_1 filters The sensitivity of the instrument is set by quinine, since the irradiated standards may slowly lose their fluorescence on frequent exposure to the ultra-violet light of the fluorometer

Irradiation of the 4 aminoquinolines is effected in a simply constructed irradiator, using an H-4 mercury arc-lamp as the light source The samples are placed in a circular rack surrounding the lamp so that they are equidistant from the lamp, and are irradiated for 3 hours A fan is used for keeping the temperature of the solutions below 35°C during irradiation

Salts in common use

Chloroquine diphosphate and dihydrochloride, amodiaquine dihydrochloride dihydrate

Physical data regarding salts

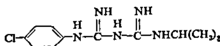
See Annex 3

Synonyms

See Annex 4

Proguanil *

Formula



proguanil N_1 p(-chlorophenyl)-N_5 isopropyl biguanide

* See Selected bibliography No 89 113 (page 110)

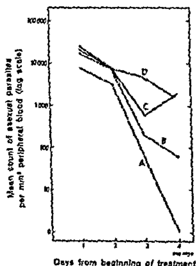
Activity in human malaria

(*a*) *Sporozoites* Probably inactive

(*b*) *Primary exoerythrocytic forms* Proguanil is highly active against the primary exoerythrocytic forms of *P falciparum* and has a fleeting inhibitory action on those of *P vivax*, its action on the presumed primary exoerythrocytic forms of *P malariae* is unknown It is thus a powerful drug for *causal prophylaxis* in falciparum malaria

(*c*) *Asexual blood forms* Active against the asexual blood forms of all species of human malaria parasite It will achieve *clinical cure* in all forms of malaria, with *radical cure* in most falciparum infections, but the clinical response is slow, and its use for the treatment of an acute malarial attack is not recommended It is a good *suppressive* of all forms of malaria, often with *suppressive cure* in falciparum infection It appears to act by inhibiting nuclear division

FIG 6 PARASITAEMIA IN 268 CASES OF ACUTE FALCIPARUM MALARIA TREATED IN MALAYA WITH PROGUANIL ILLUSTRATING A DEVELOPING RESISTANCE IN THE SCHIZOGONIC BLOOD FORMS



		cases
A =	proguanil single dose 100 mg (1947-8)	26
B =	proguanil single dose 250 mg or 300 mg (1948)	40
C =	proguanil single dose 250 mg or 300 mg (1949)	74
D =	daily 300 mg (standard course) (1950-1)	128
	total	268

Data from Malaria Research Division, Institute for Medical Research Federation Malaya 1946-7

FIG. 7 FEVER IN 913 CASES OF ACUTE FALCIPARUM MALARIA TREATED IN MALAYA WITH PROGUANIL OR QUININE

	cases
A =	26
B =	40
C =	74
D =	128
E =	645
total	913

Data from Malaria Research Division Institute for Medical Research Federation of Malaya 1946 7

(*d*) Gametocytes Proguanil has little apparent effect on the production, numbers, or morphology of the gametocytes of *P falciparum*, but in appropriate doses the drug inhibits the later development of sporogonic forms in the mosquito Mosquitos fed on gametocyte carriers receiving therapeutic doses of proguanil do not become infective—an inhibitory effect on sporogony which lasts for varying periods up to ten days after the last dose, depending on the total quantity administered Sporogony in *P viax* is similarly affected Proguanil is thus a valuable drug for *sporontocidal prophylaxis*

(*e*) Secondary exoerythrocytic forms Probably inactive, and hence a poor drug for *radical* or *suppressive cure* in vivax malaria Its effect on the presumed secondary exoerythrocytic forms of *P malariae* is unknown

(*f*) General The outstanding virtues of proguanil are its extremely low toxicity, wide range of action, and relatively low cost It is highly active as a causal prophylactic in falciparum malaria, is a good general suppressive, has a marked inhibitory effect on the transmission of malaria by mosquitos, but is not sufficiently rapid in action for treatment of the acute attack in non immune subjects Its greatest drawback, a tendency to provoke resistance, is discussed in chapter 4 (page 59)

Toxicity

At the therapeutic dosage the toxicity of proguanil is very low, abdominal discomfort, loss of appetite, vomiting, and diarrhoea may be caused by doses of the order of 1,000 mg daily, more rarely, haematuria may be produced by such gross over dosage

Contraindications

No contraindications are known other than the presence in the area of strains resistant *either* to proguanil or pyrimethamine (see chapter 4, page 64)

Absorption, elimination, plasma concentration

Absorption is rapid, elimination is fairly slow, mainly in the urine, in which the drug may be detected for several days after the last dose About 40% is excreted in the urine and faeces, some of the remainder is converted into an active metabolite Peak concentrations in plasma are attained about four hours after oral administration The concentration in the red cells is from four to eight times greater than in the plasma Plasma levels fall below the level of accurate estimation within a week, even after heavy and prolonged dosage

Dosage and route of administration

See chapter 5

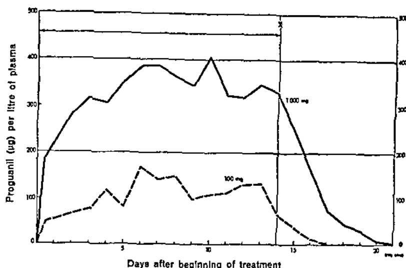
Test for estimation in body fluids

A simple test for proguanil in the urine has been devised by Gage & Rose[99]

Reagents

(*a*) Copper sulfate analytical reagent (AR), 500 mg, and ammonium chloride AR, 1,330 mg, in 100 ml of distilled water

FIG 8 CONCENTRATION OF PROGUANIL (GROUP MEANS) IN PLASMA DURING ORAL TREATMENT WITH 100 mg AND 1,000 mg DAILY



X = end of treatment

After Adams et al [44]

(*b*) Sodium diethyldithiocarbamate 0 1% aqueous solution (the solution does not keep for more than a fortnight)

(*c*) 1 N NaOH

(*d*) Benzene the commercial grade redistilled is satisfactory

Procedure

(*a*) Mix 2 ml of urine, 1 ml of copper reagent, and 1 ml of the caustic soda solution in a stoppered tube and allow to stand for a few minutes

(*b*) Add 5 ml of benzene and shake for 2 minutes Decant or pipette off the benzene into a second tube, wash with 1 ml of water, and transfer to a third tube

(*c*) Shake with 1 ml of sodium diethyldithiocarbamate solution for 1 minute

The intensity of the golden yellow colour is a measure of the amount of proguanil

Salts in common use

Monohydrochloride, acetate, lactate

Physical data regarding salts

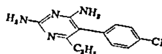
See Annex 3

Synonyms

See Annex 4

Formula

Pyrimethamine *



pyrimethamine 2 4-diamino-5 *p*-chlorophenyl-6-ethylpyrimidine

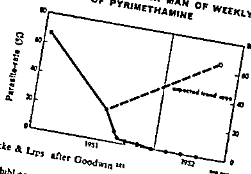
Activity in human malaria

(*a*) Sporozoites Probably inactive

(*b*) Primary exoerythrocytic forms It is thought that pyrimethamine may have some effect against these forms, but the degree of such action has not yet been defined

(*c*) Asexual blood forms Active against these forms in all types of malaria, producing *clinical cure* in all and *radical cure* in most cases of *P falciparum* infection Its action is, however slow, and it is therefore not recommended for treatment of the acute attack Dose for dose, pyrimethamine is the most powerful *suppressive* agent known *suppressive cure* is achieved against *P falciparum* infection and sometimes against *P vivax* Like proguanil it appears to act by inhibiting nuclear division

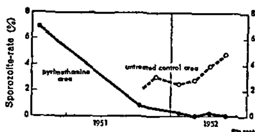
FIG 9 EFFECT ON PARASITE RATE IN MAN OF WEEKLY 25-mg DOSES OF PYRIMETHAMINE



Data from Vincke & Lips after Goodwin

* See Selected bibliography No 114-130 (page 111)

FIG 10 EFFECT ON SPOROZOITE RATE IN MOSQUITOS OF WEEKLY 25-mg DOSES OF PYRIMETHAMINE



Data from Vincke & Lips after Goodwin [131]

(*d*) Gametocytes There is no apparent effect on the production, number, or morphology of gametocytes, but the action of the drug inhibits subsequent sporogony in the mosquito, resulting in *sporontocidal prophylaxis*

(*e*) Secondary exoerythrocytic forms Active against certain strains of *P vivax*, although the exact conditions necessary for such action, in dosage and time, are not clearly defined Its effect against similar presumed stages of *P malariae* is unknown

(*f*) General Pyrimethamine is a potent drug of extraordinary effectiveness against erythrocytic parasites Its chief characteristics are (1) small weekly doses can effect complete *suppression* of quartan malaria and *suppressive cure* of vivax and falciparum malaria, (2) by inhibiting sporogony it prevents transmission of malaria by mosquitos, (3) it is tasteless and therefore easy to administer to children, (4) it is relatively inexpensive Its limitations are (i) that its action is too slow to warrant its use for treatment of an acute malarial attack in a non immune subject, (ii) drug-resistance may develop in the field, if it is administered in insufficient dosage (see chapter 4)

Toxicity

At the recommended dosage toxicity is very low, long term administration of 25 mg daily may result in a megaloblastic type of anaemia, but remission is rapid when the drug is discontinued

Contraindications

No contraindications are known other than the presence in the area of strains resistant *either* to pyrimethamine or to proguanil (see chapter 4, page 64)

Absorption, elimination, plasma concentration

Studies in rhesus monkeys utilizing doses above those recommended for man have led to the following conclusions. Absorption of pyrimethamine from the intestinal tract is relatively slow but essentially complete. It is localized to a moderate degree in the lung, liver, kidney, and spleen. About 20% of the drug administered can be recovered in the urine; this represents metabolic products and unchanged drug. The drug does not ordinarily accumulate in the plasma. Peak concentrations following oral administration are reached in approximately two hours.

Dosage and route of administration

See chapter 5.

Test for estimation in body fluids

At recommended dosages, plasma levels are too low for accurate determination; details of the test, therefore, are not included here. Those interested in the methyl orange test, modified for determining pyrimethamine concentration in body fluids, are referred to Schmidt, Hughes & Schmidt.[128]

Salts in common use

Pyrimethamine is prescribed as base, not as a salt.

Synonyms

See Annex 4.

CHAPTER 4

DRUG-RESISTANCE IN MALARIA *

One of the limiting hazards in the progress of ch [illegible]
flexible response [illegible]
seeks to destroy [illegible]
parasite, be it virus, bacterium, protozoon, or metazoon, must adapt or perish The drug in the host tissues may impose on the parasite metabolic demands which are beyond its capacity for individual or group adaptation: the parasite is then "drug-sensitive" and will remain sensitive The parasite, on the other hand, may adapt itself to the new chemical environment, and to the extent of its successful adaptation it will become "drug-resistant"

Drug resistance from the adaptation of living organisms to substances which normally destroy them or prevent their growth has been known for many years Kossiakoff,[152] in 1887, showed that bacteria could be "trained" to grow in media containing antiseptics, and two years later Massart [155] proved that flagellates could be adapted to resist concentrations of sodium chloride normally toxic Renewed interest in this interesting phenomenon was aroused with the discovery by Ehrlich, in 1908, that trypanosomes exposed to sublethal doses of trypanosomocidal drugs become resistant, and the later studies of Warrington Yorke and his colleagues brought the problem of drug-resistant trypanosomiasis to a sharp focus, but the wider implications of this work were not fully realized, and only with the discovery of acquired bacterial resistance to the sulfonamides, penicillin, and streptomycin, has drug-resistance made any serious impact on treatment Today, it seems, drug-resistance may be the rising price that has to be paid for the quickening tempo of chemotherapeutic advance

Significant drug-resistance in malaria is a recent phenomenon No important antimalarial drug used before the end of the second World War was known to induce serious resistance Quinine, pamaquine, and mepacrine, the mainstays of malaria therapy, had never given serious cause for anxiety on this score, and it seemed that the malaria parasite might lack the capacity for adaptation which certain bacteria were then beginning to show towards the sulfonamides and penicillin But the discovery, in 1947, of acquired resistance to proguanil in the avian parasite *P. gallinaceum*

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* See Selected bibliography, No 131-173 (page 114)

sounded a note of warning [132, 168] The asexual blood forms of this species could be "trained"—if we may use the word "trained" with no implication of the mechanism involved—to resist high doses, and the resistance was stable enough to survive passage through mosquitos In quick succession other species of *Plasmodium*, including *P falciparum* and *P vivax* infecting man, were shown to share this capacity for adaptation to proguanil, and for the first time drug resistance in malaria appeared as a significant clinical problem

Definitions

The expression "drug resistant malaria" has a deceptive simplicity Malaria parasites may be said to "resist" when exposure to a drug in the tissues of the host leaves at least some of them unharmed They resist small doses of quinine and they resist many drugs which are lethal to other minute forms of life but have no interest as remedies for malaria Resistance in this wide sense has little relevance to the clinical problems of drug resistant malaria, and in this discussion we shall consider it only in relation to drugs which, administered to the vertebrate host in adequate and safe doses, normally destroy or contribute to the destruction of malaria parasites at some stage or other in their life-cycle

Resistance within the limits of dosage tolerated safely by the host may be absolute, or it may be relative to a normal sensitivity Sporozoites are completely refractory to the largest doses of quinine the host will stand, within this limit their resistance is absolute Resistance in particular geographical strains, on the other hand is relative to the general sensitivity of other strains, and acquired resistance is relative to the initial sensitivity of the species before there has been significant drug contact

Resistance to a drug is conveniently expressed in terms of the dosage administered with safety to the host If, for example, the lowest lethal concentration for a parasite is attained on first exposure by a host dosage of 5 mg, but later only by 500 mg, the parasite is said to have acquired a hundredfold resistance An arbitrary limit to resistance is reached when the dose which is lethal to the parasite is no longer safe for the host

Natural resistance within a species

All malaria remedies are selective in their action The parasite is not uniformly sensitive to drugs throughout its life-cycle, and at particular stages it may show a high degree of natural resistance Sporozoites, possibly from their fleeting exposure in the human host, seem to resist all known drugs, and to most drugs the tissue forms are equally refractory With few exceptions, the asexual blood forms in all species are sensitive

to all the accepted malaria remedies, while the gametocytes show marked specific differences in this respect Table I illustrates this natural resistance within a species

TABLE I NATURAL DRUG RESISTANCE AT VARIOUS STAGES IN THE LIFE CYCLE OF *P FALCIPARUM* AND *P VIVAX*

	P falciparum				*P vivax*			
	sporozoites	tissue forms	blood forms (asexual)	gametocytes	sporozoites	tissue forms	blood forms (asexual)	gametocytes
Quinine	R	R	—	R	R	R	—	—
Mepacrine	R	R	—	R	R	R	—	—
Chloroquine	R	R	—	R	R	R	—	—
Pamaquine	R	—	R	—	R	—	—	—
Proguanil	R	—	—	—	R	R	—	—
Pyrimethamine	R	—	—	—	R	—	—	—

R = resistant

This selective resistance within a species is a fixed character in no way related to earlier exposure to a drug It poses no novel problem and its acceptance has long been implicit in the planning of malaria therapy

Resistance in geographical strains

Malarial infections from different parts of the world do not always respond equally well to the same treatment, and it seems that geographical strains of the same species of parasite sometimes differ in their sensitivity to particular drugs The reason for these strain differences is not always clear They may possibly express a natural variation related to geographical isolation, but the influence of previous contact with drugs can seldom be excluded

Resistance acquired by previous drug contact

A high degree of drug resistance in a species normally sensitive is probably always an adaptive change related to previous exposure A thousandfold resistance to proguanil has been produced experimentally in the blood forms of *P vivax* [141] Malayan strains of *P falciparum*, sensitive in 1947 to a single dose of 100 mg of proguanil, were resistant to many times this dose two years later [98] The asexual blood cycle of the monkey

parasite, *P cynomolgi*, is naturally sensitive to pyrimethamine, but highly-resistant strains may appear under laboratory conditions [127]

The range of drug-resistance

All forms of the malaria parasite normally sensitive to drugs may in theory become resistant The problem of drug resistance must hence be considered in relation to the asexual tissue forms, to the asexual blood forms, and to the gametocytes, and even, by a carry-over effect on the gametocytes, to the sporogonic forms in the mosquito

Resistance to the Common Antimalarial Drugs

Quinine

The parasites of human malaria are sensitive to quinine at important but restricted phases in their life-cycle The schizogonic blood forms of all species infecting man are sensitive, and so are the gametocytes of *P vivax*, *P ovale*, and *P malariae*

A lessened sensitivity to quinine in the asexual blood forms of *P falciparum*, presumed to be natural, has been reported from several parts of the world An Italian strain of *P falciparum* has been shown to be much less sensitive to quinine than an Indian strain observed under the same conditions,[118] and a Panamanian strain is reported to have shown a mild relative resistance,[140] the New Guinea Chesson strain of *P vivax* seems to be less sensitive than the McCoy strain indigenous in the United States of America [87] The "quinine resistant" malaria reported from Mesopotamia after the first World War may possibly have some such explanation, but quinine-resistance was then held to explain a poor clinical response for which there were other possible causes

Acquired resistance to quinine in human malaria is rare, if indeed it occurs at all Certain writers refer to a "dulling of the quinine effect", observed during the first World War, but little support for this view has appeared since, and Fletcher,[142] with this wartime experience in mind, found that quinine-resistance in cases observed in Malaya vanished when he gave the drug with his own hands In avian malaria, experimental attempts to induce resistance by intensive quinine treatment have either failed [153 169] or have achieved no more than a slight resistance [169] A trifling cross-resistance between pamaquine and quinine has been reported [159]

Pamaquine

Prolonged exposure to pamaquine may induce a slight resistance in the asexual erythrocytic forms of certain avian and mammalian species of

Plasmodium,[133, 139, 143, 144, 156] but acquired resistance in species infecting man has not been reported. The asexual blood forms of *P. falciparum* have a marked natural resistance to pamaquine. Pentaquine, isopentaquine, and primaquine, 8-aminoquinolines related to pamaquine, are presumed to have similar tendencies. Pamaquine resistance in *P. gallinaceum* confers no resistance to mepacrine, chloroquine, or proguanil, but pamaquine-resistant strains may be slightly resistant also to pentaquine and quinine.[139]

Mepacrine

Experimental attempts to induce resistance to mepacrine in avian and mammalian species have failed,[132, 133, 160, 168, 169] and the risk of acquired mepacrine-resistance in human malaria seems to be small. There is an isolated report, however, of a relative resistance to mepacrine in strains of *P. falciparum* observed in the Aitaipe-Wewak area of New Guinea. These resisting strains regularly produced overt malaria in volunteers receiving 100 mg of mepacrine daily, a suppressive dosage which was efficient elsewhere in New Guinea and, indeed, in other parts of the world. This resistance seems to have been acquired, for the resisting strains were isolated from a selected group of patients repeatedly given a standard quinine-mepacrine-pamaquine treatment for recrudescent attacks. Under the same conditions there was no evidence of resistance in *P. vivax*.[59]

Chloroquine

Like mepacrine, this drug has little tendency to induce resistance in malaria parasites exposed to its action. Experimental attempts to induce resistance in the avian parasites *P. gallinaceum* and *P. lophurae*, in the monkey parasite *P. cynomolgi*, and in *P. vivax* of man, have been unsuccessful.[138, 141, 161, 166]

Amodiaquine

Resistance to amodiaquine has not been reported and on chemical and pharmacological grounds any tendency in this direction seems improbable. An attempt to induce resistance in *P. lophurae* (chicks) was not successful.[288]

Pyrimethamine

Experience of pyrimethamine in the treatment and prevention of human malaria is still limited, and comparatively little is known of resistance to this drug in the species infecting man. Resisting strains have been produced experimentally in *P. cynomolgi*,[127, 148b] *P. knowlesi*,[123b] and *P. vivax*[122]

A mild resistance in *P falciparum* has been reported from an area in Malaya where proguanil resistance is well established,[170] and Jones, experimenting on himself, has proved that a proguanil-resistant falciparum strain from this area was resistant also to pyrimethamine [119] Experience in Kenya shows how quickly resistance in this species may appear and spread after mass treatments [150]

Proguanil-Resistance

As noted earlier, the tendency of proguanil to produce resistance has considerably modified early optimism and its place in the future patterns of therapy is now less certain The problem of proguanil resistance has been very extensively studied since it was first reported in 1947

In the laboratory a resistance to proguanil appears when parasites are exposed to significant but sublethal doses of the drug, usually with repeated blood passage from host to host, conditions which are exceptionally favourable for the emergence of resistant strains From later work, however, it seems that a resistance in *P falciparum*, *P vivax*, and *P malariae* may appear under the less favourable circumstances of field and hospital practice

Range

Resistance to proguanil may occur, theoretically, at any or all of the three stages in the life-history of the parasite on which it acts

1 *Exoerythrocytic forms* The exoerythrocytic forms of *P vivax*, and probably those of *P malariae* and *P ovale*, are naturally resistant to proguanil, but the pre-erythrocytic forms of *P falciparum* in the tissues are highly sensitive It seems, however, that this sensitivity may be lessened in falciparum strains with established resistance in the erythrocytic cycle Primary falciparum infections have been acquired by newcomers to Malaya naturally exposed to resistant strains and alleged to have taken 100 mg of proguanil daily for weeks or months beforehand, moreover, a human volunteer, bitten by mosquitos infected from a resistant Malayan strain, developed overt falciparum malaria 11 days later despite regular daily doses of 100 mg of proguanil during the incubation period [167] Resistance has also been reported in the pre-erythrocytic forms of the monkey parasite, *P cynomolgi*,[147] and of the avian parasite, *P gallinaceum* [115a]

2 *Asexual blood forms* Acquired resistance to proguanil in the asexual blood forms has been reported not only in avian species of *Plasmodium*, but in three of the species infecting man (table II) Prolonged contact with proguanil under appropriate experimental conditions may induce a resistance so high that the tolerance of the parasite for the drug may become

greater than that of the host[141] Resistance has also been encountered in the course of clinical or preventive practice in malarious countries, though the recorded incidence is low; moreover, the resistance has been slow to develop and moderate in degree.[98, 113, 140a, 140b, 141a]

TABLE II PROGUANIL-RESISTANCE IN THE ASEXUAL BLOOD FORMS OF VARIOUS SPECIES OF *PLASMODIUM*

Species	Bib No	How acquired	Months to acquire	Degree	Transmission through mosquitos
P gallinaceum (chick)	132	experimental	5	high	yes
"	168	"		moderate	yes
P lophurae (duck)	166	"	7	moderate	
P cynomolgi (monkey)	146	"	14	high	
"	160	"		high	yes
"	147	"	16	high	yes
P falciparum (man)	131, 162	"	10	high	yes
"	98	field conditions	24	moderate	
"	140b	natural			
P vivax (man)	163	experimental	20	high	yes
"	141		4-6	high	
"	171	field conditions	48	moderate	
P malariae (man)	100	"		moderate	

3 *Gametocytes* Resistance to proguanil, once established in the erythrocytic cycle, may extend to the gametocytes The experimental evidence on this point is scanty, but decisive Mosquitos have been infected with a proguanil resistant strain of *P gallinaceum* while the host chicks were receiving full doses of the drug,[133] and a resistant strain of *P falciparum* from a gametocyte carrier receiving 100 mg of proguanil daily has [illegible][100] It is possible that [illegible]

Rate of development

Resistance to proguanil may appear quickly, or slowly, or indeed not [illegible] Under artifi- [illegible] ming of treat- [illegible] calculated to favour the survival of resisting organisms, a high tolerance to proguanil in the asexual blood forms of *P falciparum* and *P vivax* may appear within a few months

The usual conditions of clinical or preventive practice in malarious countries are never so favourable for the production of resistance as are those of the laboratory, they are seldom likely to be decisively unfavourable The possible trend of events in malarious regions where proguanil is used freely may be illustrated by experience in Malaya Here the drug was first used for treatment and prevention early in 1947, and records of the proguanil response in acute infections contracted in a single district have been kept for nearly six years At first, a single dose of 100 mg of proguanil would terminate acute falciparum attacks The first recorded failure of single dose therapy was in October 1948 and the first failure of a standard therapeutic course (300 mg × 7) in April 1949 By 1950, nearly half of the falciparum infections treated failed to respond to a full therapeutic course In *P vivax*, a definite proguanil resistance was proved only in January 1951, and its incidence has remained low Resistance in *P malariae* has not yet been recognized in Malaya but has been reported from Indonesia [100]

Proguanil suppression in Malaya, started experimentally in December 1946, has since been used as a standard method of control on many rubber estates and by the Security Forces There was good evidence that a 100-mg dose twice a week was very efficient in the early days Five years later, in certain districts there were indications that a daily suppressive dose of 100 mg would sometimes fail, though by and large the drug was still thought to be a very useful suppressive

Stability

Once established, proguanil resistance in the asexual blood forms appears to be fairly stable It may persist through many asexual generations, and it may be unchanged by a transfer of the parasite to a fresh host whether by blood or mosquito-passage Resistance in *P gallinaceum* has been shown to last for at least a year without further exposure to the drug,[135] and to survive serial passage through mosquitos,[133] while there is suggestive evidence that resistance in *P knowlesi* may persist for at least eight months [123] Resistant strains of *P cynomolgi*, *P falciparum*, and *P vivax* have been shown to remain resistant after mosquito transmission to a fresh host [147, 150, 162, 163]

Spread under field conditions

In latent infections, with few parasites in the peripheral blood, attempts to induce resistance have been unsuccessful [134, 159] It may thus be assumed that the primary factors in causation are under-dosage and significant parasitaemia, operating together, and, under field conditions, found particularly in the under treated acute attack and in the under suppressed

greater than that of the host [141] Resistance has also been encountered in the course of clinical or preventive practice in malarious countries, though the recorded incidence is low, moreover the resistance has been slow to develop and moderate in degree [98, 113, 140a, 140b, 144a]

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	160			high	yes
	147		16	high	yes
P *falciparum* (man)	131 162		10	high	yes
	98	field conditions	24	moderate	
	140b	natural			
P *vivax* (man)	163	experimental	20	high	yes
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	171	field cond tions	48	moderate	
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Resistance to proguanil may appear quickly, or slowly, or indeed not at all, depending on the conditions of exposure to the drug Under artificial conditions, with deliberate under dosage, with careful timing of treatment, and with a serial transfer of parasites to fresh hosts calculated to favour the survival of resisting organisms, a high tolerance to proguanil in the asexual blood forms of P *falciparum* and P *vivax* may appear within a few months

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smouldering infection The most fertile source of resistant parasites is likely to be the under-treated attack in which a parasite population of the order of 10^{9}-10^{11} or more is exposed to a dose of drug sufficient only to destroy the more sensitive members

Suppressive proguanil-therapy is likely on theoretical grounds to pose a lesser problem of resistance, for parasitaemia in the under suppressed infection will usually be low But here again under-dosage from irregular administration will greatly raise the odds With missed doses, parasitaemia may rise to a clinical level and the dual effect of a high concentration of parasites and a low concentration of drug come into play

Resistance developing from under-dosage is at first a personal problem, restricted to the subjects whose parasites have become proguanil tolerant In time the resisting parasites would die out were they not transferred to a new host Resistance becomes a community problem when the resisting strains are diffused by mosquitos The extent of spread is determined by [illegible]

parasites in mosquitos, the transmission of resisting strains, no less than their initiation, is likely to be related to under dosage

Recognition

Proguanil resistance may declare itself in various ways

(*a*) The failure of a single dose to achieve in mild acute infections a remission of symptoms and to eliminate the schizogonic cycle in the blood *is evidence of a slight loss of sensitivity* This was the earliest indication of a developing resistance in Malayan strains of *P falciparum* Today, however, routine single dose proguanil therapy is not recommended and this method of detecting early resistance has no more than experimental interest The failure of a standard therapeutic course of 300 mg daily in acute infections to clear asexual parasites from the blood within seven days indicates a growing resistance in the schizogonic blood forms, but again this method of assessing resistance will usually be experimental, for proguanil alone is seldom recommended today for the treatment of the acute attack

(*b*) The occurrence of overt malaria in inhabitants of endemic areas who are known to have taken regular suppressive doses of proguanil may suggest that resistance is developing, although perhaps only in the asexual blood forms of the parasite

(*c*) The occurrence of overt malaria in newcomers who have taken 100 mg proguanil daily without fail since arrival in the malarious area suggests the transmission of parasite strains which are resistant to proguanil

at various stages of their life-cycle The first suspicion of resistance in the pre erythrocytic forms of certain Malayan strains of *P falciparum* arose in this way The difficulty is that one can seldom be certain that the proguanil has been taken with unfailing regularity

(*d*) Resistance at the sporogonic stage cannot be assessed by simple clinical means The conditions of transmission in most malarious countries are too complex, and the only valid evidence is likely to be that which comes from mosquitos infected experimentally in the laboratory

Prevention

Proguanil resistant parasites are not likely to arise in the individual subject if the schizogonic cycle in the blood is permanently interrupted by efficient treatment or inhibited by efficient suppression They cannot be transmitted and spread in the community if the continued development of the gametocytes is inhibited by adequate therapy, clinical or suppressive, for every infected person In most malarious countries this is possibly a counsel of perfection The occasional resisting strain is likely to emerge in any community using proguanil on a large scale and lacking a high level of medical organization Whether the resisting strains are few or many, whether they die out or spread, must finally be determined by the prevailing standards of treatment, suppression, and mosquito control Treatment must be good enough to eliminate asexual parasites from the blood, and continued long enough to sterilize gametocytes Suppression must be regular enough to prevent the transient bursts of parasitaemia which may come with missed doses

The fact that resistance to proguanil is most likely to arise when a large parasite population is exposed to, but not eliminated by, the drug is in itself a sufficient reason why acute infections should not be treated with proguanil alone When the drug is used for malaria suppression, resistance is likely to arise only when the plasma concentration falls low enough to permit an active proliferation of parasites Irregular dosage is likely to be the common cause, and the key to prevention probably lies in a good suppressive discipline For a time the loss of effect from early resistance can be met by an increase in dosage—this is apparently the situation in parts of West Africa—but a further rise or spread of resistance would necessitate an immediate change of drug

It is not always easy to arrive at a decision when resistance is mild or sporadic, and when proguanil, though still a useful suppressive, sometimes fails What margin of failure is to be considered tolerable in the light of the other virtues of the drug? To what extent should we weigh in the balance the great potential value of proguanil as a safe causal prophylactic in falciparum infection and as a non toxic sterilizing agent for mosquito

infections? This is a problem which faces public health authorities in some territories today, and there is no clear answer We may take the view that the most efficient suppressive drug should always be the drug of choice the 4-aminoquinolines and mepacrine are better suppressives than proguanil under the conditions prevailing, for example, in certain parts of Malaya Or we may regard the direct action of proguanil on the pre-erythrocytic and sporogonic forms as a powerful asset not to be discarded lightly A deciding factor might well be the proguanil sensitivity of the prevailing strains at the pre-erythrocytic and sporogonic phases of growth Should this sensitivity be lost, there would be a strong indication for a change-over to another drug

Cross-Resistance

The fear that a resistance to one drug might confer on malaria parasites a general tolerance to other antimalarial drugs has proved to be ill founded Cross-resistance certainly occurs, sometimes to a marked degree, but the phenomenon presents no clinical problem which cannot be met simply by a change of drug Experimental evidence suggests that the only important compounds to which malaria parasites may show a significant cross-resistance are proguanil, pyrimethamine, and the sulfonamides (table III)

Cross-resistance between proguanil and the sulfonamides has much theoretical interest, but the sulfonamides are not used as malaria remedies, and there is little danger of proguanil-resistant malaria from sulfonamide therapy in other diseases

The extent and significance in human malaria of a cross resistance between proguanil and pyrimethamine has still to be assessed Pro- [illegible]

resistance in the local falciparum strains Resistance to pyrimethamine in the Chesson strain of *P vivax* confers a partial resistance to proguanil [123] This disturbing cross-resistance might well restrict the use of proguanil and pyrimethamine in territories where resistance to one of them is known to occur

The three drugs, proguanil, pyrimethamine, and sulfadiazine, all seem to act on malaria parasites in much the same way—by inhibiting nuclear division They all tend to induce a high resistance in parasites exposed to their action, and resistance in any one of them may extend to one or more of the others Quinine, mepacrine, and the 4-aminoquinolines do not induce significant resistance nor are they involved in cross-resistance They are chemically unrelated to proguanil, pyrimethamine, and the sulfon-

TABLE III CROSS RESISTANCE BETWEEN ANTIMALARIAL DRUGS

Species	Bib No	Primary acquired resistance	Associated resistance	Resistant strain still sensitive to
P gallinaceum	134 136 137	sulfadiazine	proguanil other sulfonamides	quinine mepacrine pamaquine
"	168	proguanil	—	quinine mepacrine sulfadiazine
	136 157	proguanil	sulfadiazine (slow)	
"	139	pamaquine	pentaquine quinine (slight)	proguanil mepacrine sulfadiazine chloroquine
P berghei	45	sulfadiazine	proguanil (slight)	
"	48	proguanil	pyrimethamine (slight)	
P lophurae	166	proguanil		pamaquine quinine mepacrine chloroquine amodiaquine
P cynomolgi	147 160	proguanil		chloroquine mepacrine pentaquine sulfadiazine
"	127	pyrimethamine	proguanil	chloroquine
P knowlesi	165	proguanil	pyrimethamine	
P falciparum	125 149	proguanil	pyrimethamine	
P vivax	141	proguanil		chloroquine
	122	pyrimethamine	proguanil	chloroquine

amides, and they probably act on malaria parasites by a different metabolic route Schmidt and his colleagues have drawn attention to a possible parallel with the bacteriostatic sulfonamides and the bactericidal penicillins, and suggest that resistance in malaria parasites develops in relation to drugs which inhibit the growth of the parasites, rather than to drugs which destroy them [160]

Origin and Mechanism of Drug-Resistance

Drug resistance in human malaria may be explained in various ways We may assume that the new chemical environment imposed by the drug induces a change in all the parasites enabling them to find a metabolic pathway of escape from its lethal effects, this is the theory of physiological adaptation Or we may assume that resistant parasites arise by chance as

rare mutants and that the drug is merely a selective agent, this is the theory of spontaneous mutation. Or, again, we may accept mutation as the key to resistance, but assume that mutations are bound up in some way with exposure to the drug, this may be called the theory of induced mutation. Yet again, we may accept the simple theory advanced by Yudkin,[173] which assumes that cell division does not necessarily distribute the systems responsible for resistance equally between the daughter cells. Repeated divisions would produce a clone of cells with the average resistance of the parent cell, but with a distribution of greater or lesser resistance around that of the parent cell. The drug might then have the effect of destroying the cells of lesser resistance, with a progressive shift of the average towards a higher resistance, this is the theory of clonal variation with selection.

Physiological changes directly induced by environment involve potentially all members of an exposed population. They are thought to be non-inheritable and hence impermanent. Changes arising from mutation, on the other hand, involve the genetic or heredity producing mechanism of the cell and are passed on from generation to generation. They appear only in a minute proportion of cells, and tend to be stable and permanent, finding expression in the population as a whole by the selective influence of environment and they are liable to occur as a sudden event, or discontinuous "step wise" series of events, rather than as a gradual and continuing process. Clonal variation would similarly be expected to produce inheritable change, tending to permanence, but occurring rather as a smooth and continuing process.

The mechanism of drug resistance

The observed phenomena of drug resistance in malaria, while suggesting a genetic origin, give little clue to the mechanism of change. The character of resistance is carried throughout the life-cycle of the parasite in vertebrate and invertebrate hosts, it continues unchanged from generation to generation in the asexual blood forms, it tends to persist when the exciting stimulus has been withdrawn, and it is readily produced only in parasite populations large enough to include a few resistant members. An abrupt appearance of resistance has been reported but a rather gradual development seems to be more usual. These are phenomena for which spontaneous mutation, induced mutation, or clonal variation, could equally provide satisfying explanations, though it is perhaps significant that the drugs which give rise to serious resistance are those which apparently interfere with the division of nuclear chromatin. Beyond this general statement we cannot go, for genetic studies of malaria parasites are exceedingly difficult, and little work seems to have been done on this subject.

The nature of resistance

If there is little assurance as to the origin of resistance in malaria parasites, there is even less regarding the changes within the parasites which enable them to resist The problem is bound up with the metabolism of the parasites and with the precise mode of action of drugs, and existing knowledge on these subjects is still fragmentary

Drug resisting parasites are clearly different in some way from those which do not resist The differences are not evident in their form, nor, in the absence of the drug, in their behaviour They are subtler differences related to the metabolism of the parasite cell We may conceive, for example, that the permeability of the parasite to certain drugs is subject to variation Resistance might then arise by the selection of variant parasites which deny access to the interior of the cell The resistance of trypanosomes to organic arsenicals has been explained in this way Or variation might involve the enzymic constitution of the parasite cell, with resistance appearing where, for example, a variant parasite is able to dispense with an enzyme system normally subject to interference by the drug If, as we may suppose, a drug acts by disturbing the synthesis or utilization of some essential metabolite, the parasites may conceivably evade this action (*a*) by an increased production of the metabolite, or (*b*) by finding an alternative pathway for its synthesis, or (*c*) by a capacity to grow in its absence The sulfonamides appear to act on certain bacteria by competing with the metabolite *p*-aminobenzoic acid in an essential enzymic system, while an increased production of this metabolite is associated with sulfonamide-resistance Can we relate this evidence to sulfonamide-resistance in malaria? Pteroylglutamic acid, a product of the metabolism of *p*-aminobenzoic acid, inhibits the action of sulfadiazine and proguanil in certain forms of malaria [115] May we then presume that resistance to these drugs is related to parasite variations involving the synthesis of, or need for, pteroylglutamic acid? Evidence in this highly complex field is steadily accumulating, but whether, or to what extent, these or similar mechanisms come into play in drug resistant malaria is not yet clear

Commentary

The main phenomena of drug resistance in malaria may be stated in a few words At particular phases in their life-cycle, malaria parasites evolve a means of surviving in the presence of drugs which normally destroy them The resistance seems to be causally related to the exposure, usually prolonged and intermittent, of large parasite populations to a near letha dose of drug The resistance is inheritable and fairly stable It involves

mainly the schizogonic forms in the blood, but in some species it occurs also in the pre erythrocytic forms, and in the gametocytes The drugs which excite resistance are those which appear to act by inhibiting nuclear division—proguanil, pyrimethamine, and the sulfonamides Cross resistance between these drugs may occur Drugs like quinine, mepacrine, chloroquine, and pamaquine—which appear to act in some other way—do not give rise to significant resistance

The most satisfying theories assume that resistance is due to the selective survival of resisting organisms arising by mutation or by "clonal variation" Whether the resisting organisms appear at random or are changed in some way by the drug we do not know Nor do we know in what way the parasites are changed Do they resist the penetration of the drug, or does resistance depend on their enzymic constitution ? Have the resistant parasites some other pathway for the synthesis of a necessary metabolite, a synthesis normally arrested by the drug ? If so, is the same enzyme system involved at the three phases of the life-cycle in the tissues, the blood, and the mosquito's stomach ? Having arisen at some point, does resistance extend throughout the cycle ? Is resistance a permanent quality or will it die away in time when the exciting stimulus is withdrawn ? These questions, and the doubts which they engender, emphasize the need for a better understanding of the intricate problems still awaiting solution

CHAPTER 5

THE CLINICAL USE OF ANTIMALARIAL DRUGS *

Chemotherapy has scored some of its greatest successes in the treatment of human malaria There are few infections more responsive to well-directed therapy, and fewer in which therapy can be applied with results so satisfying on so wide a front The first, perhaps still the greatest, success came with the discovery three centuries ago that the bark of cinchona would "cure" certain fevers The patient sick with the ague took the remedy, and was soon well again—the simplest and still the main clinical approach to malaria chemotherapy But the fever often came back, and as early as the 17th century Sydenham had broadened this simple concept to embrace the idea of prevention He gave the bark to persons who expected a recurrence of the fever but who were not sick at the time After the isolation of the principal alkaloids of cinchona, the small daily dose of quinine came to be adopted as a clinical preventive

The practice of using cinchona or quinine to end the malarial attack and to prevent further clinical manifestations of the disease continued unchanged until the end of the first World War The introduction of experimental malaria therapy soon after its termination led to a clearer understanding of the natural history of malaria in man, while, as has been described, the synthesis of pamaquine in 1926 started a trickle, soon to become a stream, of new compounds lethal to the parasite New methods [illegible] alike in its curative and preventive aspects, reflects the advances achieved by laboratory research Twenty five years ago the prospects for radical prevention in falciparum infection were remote and prolonged courses of quinine were advocated for radical cure Today, well timed therapy with minute doses of proguanil will eradicate *P falciparum* at a pre-clinical stage in the human host, while a few days' therapy with one of the 4-aminoquinolines will usually cure the established infection Falciparum malaria may now be suppressed with an ease and efficiency, with a safety and economy,

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* See Selected bibliography No 174-182 (page 114)

which must surely approach the ultimate limits of advance in this direction But with vivax infection progress is less impressive We lack a safe and sure preventive, though pyrimethamine may take us a step forward, and radical cure still depends on a prolonged treatment with drugs of moderate toxicity

The Aims of Malaria Chemotherapy

1 *The life cycle of the parasite and the widening range of therapy*

From the account given in chapter 2 of the relation of its various phases to the mode of action of antimalarial drugs, it is clear that the malaria parasite lies open to attack by well directed therapy throughout most of its complex life-cycle The sporozoite alone seems to be resistant The schizogonic forms in the fixed tissues and circulating blood, the gametocytes and, through a carry-over effect, the *sporogonic forms in the mosquito*, are alike vulnerable to appropriate therapy, with differing effects on the course of infection (table IV)

TABLE IV CLINICAL RANGE OF MODERN THERAPY IN HUMAN MALARIA

Stage in life cycle of parasite	Clinical range of present day drugs
Schizogonic forms in fixed tissues	causal prophylaxis of falciparum infection before the parasites reach the blood
	radical cure of vivax infection
Schizogonic forms in the blood	termination of the acute attack
	radical cure of falciparum infection
	suppression of all forms of malarial infection
	suppressive cure of falciparum infection
	reduction in source of gametocytes with indirect effect on transmission
Gametocytes	direct effect on transmission

2 *Therapeutic resources*

The aims of malaria chemotherapy may now be more closely defined Broadly, they remain what they have always been—to cure the patient sick with malaria and to prevent malaria or its clinical manifestations under all the varied circumstances in which they may appear We think first of the individual If he is exposed to infective mosquitos we aim to protect him by sterilizing infection while it is still symptomless, if he becomes

sick with malaria, to relieve his symptoms as speedily, as safely, and as comfortably as possible, with permanent cure of his infection. If he is a symptomless carrier, we aim to eradicate the infection, or, failing this, to suppress it at a continued subclinical level. For the community we aim to break the chain of transmission by directing treatment, curative and suppressive, toward the destruction of gametocytes or to the inhibition of their production or development.

The ideal drug would meet all these demands without harm to the patient. It would be quick in action and unvarying in its effects. It would be active in all forms of human malaria, at all stages, and it would not induce resistance in the parasites. Furthermore, it would be easy to administer by the oral or by the parenteral route, and it would be stable and cheap. *No known drug satisfies all these exacting requirements, though* most of them can be met by a judicious selection of the drugs now available.

The compounds which fill a useful role in malarial therapy are all members of four chemical groups—the 4-aminoquinolines and allied compounds, the 8-aminoquinolines, the biguanides, and the pyrimidines. Table V lists the compounds on which present-day therapy is mainly based.

TABLE V. DRUGS ON WHICH PRESENT-DAY MALARIA CHEMOTHERAPY IS BASED

Chemical group	Main members of the group	Activity
4-aminoquinolines and related compounds	chloroquine amodiaquine mepacrine quinine	Essentially schizontocides. Little action on exoerythrocytic parasites, or on the gametocytes of *P. falciparum*. The most useful drugs known for treating acute malaria; all except quinine are powerful suppressives. Low toxicity. Do not induce drug-resistance.
8-aminoquinolines	primaquine pamaquine	Poor schizontocides, but active against gametocytes and against exoerythrocytic parasites. Main uses: gametocytocidal treatment and radical cure in vivax infection. Moderately toxic. Do not induce significant drug-resistance.
Biguanides	proguanil	Schizontocide and sporontocide. Active also against the exoerythrocytic forms of *P. falciparum*. Main uses: causal prophylaxis in falciparum infection, suppression and inhibition of sporogony. Non-toxic. Liable to induce drug-resistance.
Pyrimidines	pyrimethamine	Activity similar to that of proguanil, but has some action also on the exoerythrocytic forms of *P. vivax*. Main uses: as for proguanil. Low toxicity. Liable to induce drug-resistance.

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Gametocytes	*direct effect on transmission*

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The compounds which fill a useful role in malarial therapy are all members of four chemical groups—the 4-aminoquinolines and allied compounds, the 8 aminoquinolines, the biguanides, and the pyrimidines. Table V lists the compounds on which present-day therapy is mainly based.

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The Confusions of Dosage

A severe case of falciparum malaria may require 10,000 mg (150 grains) of quinine before the fever is controlled, an evanescent febrile episode in an old standing infection may be terminated by three or four tablets of aspirin A proguanil sensitive falciparum infection may be clinically cured by a single proguanil tablet of 100 mg, a resistant infection may still persist when the patient has received 50 times this amount These extreme examples illustrate the fallacies which may underlie attempts to fix arbitrary levels of dosage, suitable for all malaria infections, at all times, and in all places Confusion arises mainly from the immunity factor in the thera peutic response, from differences in the geographical strains of the para sites, and from drug resistance

1 *The immunity factor*

The response to treatment in malaria is usually, perhaps always, an expression of a dual effect The plasmodicidal effect of the drug is rein forced by a contribution from the tissue defences In the early stages of a primary infection in subjects with little immunity the contribution from the tissues may be small, in old standing infections the tissue defences may suffice of themselves to break the schizogonic cycle of the parasite Logi cally, the dose of a drug should then be related to the immune status of the subject Immunity, however, is not always easy to assess, and the dosage usually recommended is that appropriate for infection in the non immune subject Medical officers, with their special knowledge of the malaria with which they have to deal, are best able to decide whether, and to what extent, they may safely reduce the dosage ordinarily recommended for treatment and suppression

2 *Strain of parasite*

As noted elsewhere, geographical strains of malaria parasites sometimes differ in their sensitivity to a particular drug Primaquine is more active against Korean vivax strains than against the New Guinea Chesson strain, the Costa strain of *P falciparum* seems to be less sensitive to quinine and mepacrine than the McLendon strain of the same species, a Dutch strain of *P vivax* has been shown to be less sensitive to Salvarsan than the Madagascar strain, which is probably of African or Asian origin and other examples have been recorded The differences are seldom marked, and they do not appear to be common, but at least they show that a drug dosage may not necessarily have universal validity, and they may some times explain why a drug regimen which gives good results in one part of the world may be disappointing in another

3 *Drug resistance*

Dosage is normally based on the response to treatment of fully sensitive parasites Should the parasites become resistant, the recommended dosage might be seriously at fault Fallacy from this source, however, is unlikely to arise with quinine, mepacrine, chloroquine, or amodiaquine, the drugs on which the treatment of acute infection is based The only drugs giving rise to serious resistance are proguanil and pyrimethamine

4 *Age and body-weight*

[illegible]

about 110 lb (50 kg) in weight, and individuals may weigh less than 100 lb (45 kg) The calculation of dosage on a body weight basis, taking 150 lb as the norm, is probably a sound rule For children up to the age of 12 years, a modified Young's formula * gives a good approximation to the body weight dosage Children tolerate antimalarial drugs quite well, and should there be uncertainty as to the dosage for serious infection, it is wiser to give too much rather than too little

5 *Base or salt*

Another source of confusion is the practice of expressing dosage sometimes as the salt, sometimes in terms of the content of active base A proprietary brand of chloroquine is marketed as tablets of 250 mg with no mention of the amount of active base, another brand, sold as tablets of 200 mg, has the base content printed in smaller type on the label, both contain 150 mg of chloroquine base An amodiaquine tablet of 261 mg, on the other hand, contains 200 mg of active base, and no other figure appears on the label The dosage of pamaquine is even more confused an 18 mg tablet of the naphthoate and a 10-mg tablet of the dihydrochloride alike contain 8 mg of active base, but the figures which receive prominence are 18 mg and 10 mg For the older drugs, like quinine, we shall continue to think of dosage in terms of the salt, but for the newer drugs there is no good reason for the persistence of this confusing anomaly The logical course is to give all dosage in terms of the active base, no other figure should appear on manufacturers' labels Where this is not possible, the dosage in terms of salt having been established by custom, the base content should at least be stated The base content of the antimalarial salts in common use is given in Annex 2

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* Dosage for children = adult dosage × $\frac{\text{age next birthday}}{\text{age} + 12}$

6 *Comment*

The drug dosage recommended throughout this account assumes that the patient is an adult weighing about 150 lb (70 kg), that he has no significant immunity to malaria, and that the parasites have no natural or acquired resistance Under particular circumstances this dosage may be inappropriate The physician alone, from his special knowledge of these circumstances, can evaluate the modification which may be necessary

The Malaria Patient *

1. The simple acute infection

The primary clinical aim in acute malaria is to bring the attack to an end, quickly, safely, and with minimal discomfort to the patient The symptoms are due to the rapid proliferation of asexual parasites in the blood, they must be destroyed The most useful drugs for this purpose are the 4-aminoquinolines and related compounds (tables VI and VII) When these drugs are given at the recommended dosage, they may be

TABLE VI ADULT DOSAGE OF 4-AMINOQUINOLINES AND RELATED COMPOUNDS FOR THE SIMPLE ACUTE ATTACK

Drug	Dosage (mg) and days							Total
	1	2	3	4	5	6	7	
Chloroquine base or	600 + 300 a	300	300	—	—	—	—	1 500 mg
Amodiaquine base or	600	400	400	—	—	—	—	1 400 mg
Mepacrine or	200 × 5 b	300	300	300	300	300	300	2 800 mg
Quinine c	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	2 000 (30 grains)	14 000 mg (210 grains)

a Second dose 6 hours after first
b Every 6 hours
c Quinine in divided doses Some authorities reduce the daily dose to 20 grains after the first 2 days (total 160 grains)

Note The dosage of antimalarial drugs recommended by workers in different countries shows considerable variation For example in India it has been stated that a single dose of 600 mg of chloroquine or amodiaquine or a 3-day course of 20 to 30 grains of quinine daily will effect clinical cure in the majority of mild infections

* In general this account is restricted to the specific treatment of malaria Nursing management relief of special symptoms and convalescence are in accord with general principles

TABLE VII. PROPRIETARY PREPARATIONS AND SALTS OF DRUGS RECOMMENDED FOR THE SIMPLE ACUTE ATTACK

Drug	Salt	Common proprietary names	Usual preparations
Chloroquine	diphosphate	Resochin, Aralen, Aviocior	Tablets of 250 mg containing 150 mg of chloroquine base, dosage in terms of base
	monosulfate	Nivaquine	Tablets of 204 mg containing 150 mg of base or of 136 mg of salt containing 100 mg of base or of 408 mg of salt containing 300 mg of base, dosage in terms of base
Amodiaquine	dihydrochloride dihydrate	Camoquin	Tablets containing 200 mg of base, dosage in terms of base
Mepacrine	dihydrochloride dihydrate	Atebrin, Atabrine, Quinacrine	Tablets of 100 mg containing 79% of base, dosage in terms of dihydrochloride dihydrate
Quinine	dihydrochloride or sulfate	—	Acid solution, dosage in terms of salt

expected to bring about a remission of symptoms within from one to three days and to eradicate most falciparum and ovale infections Infections due to *P vivax* or *P malariae* are likely to recur The treatment of relapsing infections is discussed in a later section (page 81)

The drugs are normally given by mouth but, should the patient be unable to retain the drugs because of nausea or vomiting, the whole or some part of the dose must be given by injection In this event, oral treatment must be resumed as soon as possible Parenteral treatment is discussed in the section on grave infection (page 77)

(a) *The " loading dose "*

has been the general synthetic compounds, -nt Quinine attains a high serum concentration fairly quickly, moreover, heavy dosage would be unsound on clinical grounds, for these reasons quinine is given at a steady level throughout treatment Mepacrine and the 4 aminoquinolines, on the other hand, reach their peak concentration in the serum more slowly, a delay which is effectively overcome by " loading " the dosage at the beginning of the course There can be little doubt that therapy with the synthetic drugs is more rapidly effective today than it was with mepacrine before the second World War, and that the " loading dose " is largely responsible for the change

(b) Chloroquine

This drug is probably unsurpassed by any known remedy for the treatment of the acute malaria attack It has the same plasmodicidal range as mepacrine, but is more active and, unlike mepacrine, does not stain the skin At normal dosage, its toxicity is very low No contraindications to its use have been reported The drug is issued under various proprietary names as tablets containing 100 mg, 150 mg, or 300 mg of chloroquine base

(c) Amodiaquine

This drug closely resembles chloroquine in its antimalarial activity The differences are probably too small to be clinically significant The toxicity at therapeutic dosage is very low, no contraindications have been reported

(d) Mepacrine

The value of mepacrine in the treatment of acute malaria was attested by extensive experience of the drug gained both before and during the second World War It is reliable and rapidly effective, but not entirely free from disconcerting side effects Temporary abdominal discomfort in the first few days of therapy, and a harmless yellow staining of the skin and eyes later on, are fairly common, rarely, the drug may induce mental symptoms varying from a mild depression or excitement to a wild mania, epileptiform convulsions have been reported with parenteral administration The mental effects ("mepacrine psychoses") tend to clear up fairly

(e) Quinine

There is a prevailing tendency today to decry quinine True, quinine has defects from which the newer synthetic remedies are free it causes unpleasant cinchonism, it may occasionally precipitate blackwater fever, and it is less likely to eradicate infection But, when all is said, for the immediate treatment of the acute infection, quinine remains a remarkably safe and effective drug

For the treatment of the acute malaria attack, quinine is given in solution in capsules or as tablets of the dihydrochloride or sulfate in divided doses three or four times a day Sugar-coated tablets are less unpleasant to the taste, they are usually efficient but they carry the off chance of defective absorption Children tolerate quinine very well and

seem to need relatively higher doses than adults Serious toxic effects from therapeutic doses of quinine are extremely rare Personal idiosyncrasy, and a history or threat of blackwater fever, are the main contraindications to its use The termination of pregnancy during quinine treatment is far more likely to be due to the malaria than to quinine, but most doctors would probably wish to play for safety by using some other drug

2. The grave infection

The clinically grave or parasitologically intense malaria infection is a medical emergency demanding immediate treatment and meticulous care until the danger is past The cause is nearly always *P falciparum*, rarely *P vivax* Warning symptoms may appear with alarming suddenness in the course of a simple falciparum attack and a few hours delay may mean the difference between life and death The clinical and parasitological indications for regarding an infection as serious, or potentially serious, are coma or mental clouding, collapse, jaundice, severe vomiting or diarrhoea, high parasitaemia, and the presence of falciparum schizonts or very young gametocytes in blood films *Every falciparum infection with more than 10% of the red cells infected is serious, however mild the symptoms In these infections the microscope sometimes gives a more reliable indication of gravity than a clinical examination*

When the patient with grave infection is conscious, co-operative, and able to swallow, he may be given oral treatment with the same drugs, and at the same dosage, as for the simple attack (page 74), but even in these cases many physicians prefer to give the first one or two doses by injection for greater assurance of prompt absorption Coma, vomiting, and severe nausea are clear indications for administering by intramuscular or intravenous injection Oral therapy should be substituted for parenteral therapy as soon as the danger is passed, and the patient is able to swallow the drugs and retain them

The most effective drugs in these cases are quinine, chloroquine, amodiaquine, and mepacrine (table VIII) Conservative physicians of an older school would probably give this order of precedence, their younger colleagues would be more likely to give pride of place to chloroquine There would probably be general agreement, however, that chloroquine is a better drug than quinine for intramuscular administration

(a) *Quinine*

With the exception of mepacrine, all the drugs recommended for the treatment of grave falciparum infection may be given either by intramuscular or by intravenous injection We must remember, however, that

(b) *Chloroquine*

This drug is probably unsurpassed by any known remedy for the treatment of the acute malaria attack It has the same plasmodicidal range as mepacrine, but is more active and, unlike mepacrine, does not stain the skin At normal dosage, its toxicity is very low No contraindications to its use have been reported The drug is issued under various proprietary names as tablets containing 100 mg, 150 mg, or 300 mg of chloroquine base

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(e) *Quinine*

There is a prevailing tendency today to decry quinine True, quinine has defects from which the newer synthetic remedies are free it causes unpleasant cinchonism, it may occasionally precipitate blackwater fever, and it is less likely to eradicate infection But, when all is said, for the immediate treatment of the acute infection, quinine remains a remarkably safe and effective drug

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(a) Quinine

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TABLE VIII PROPRIETARY PREPARATIONS AND SALTS OF DRUGS RECOMMENDED FOR PARENTERAL TREATMENT IN GRAVE INFECTION (ADULT DOSAGE)

Drug	Preparation and salts	Initial parenteral therapy	
		Intramuscular	Intravenous *
Quinine	Solutions of hydrochloride or dihydrochloride	[illegible]	[illegible]
Chloroquine	Resochin Aralen and Nivaquine are available in ampoules containing 5% of salt (approximately) 1 ml = 30-40 *mg of base*	Single dose not exceeding 10 ml of 5% solution *of salt (300-400 mg of* base) Total of 900 mg of base spaced over first 24 hours Oral the*rapy as soon as pos*sible	Recommended only when there are good clinical in*dications for intravenous* infusion (see text) An effective blood level is rapidly attained by the *safer and more con*venient intramuscular route
Amodiaquine	Stable solutions not yet available	—	—
Mepacrine	Methanesulfonate	Single doses not exceeding 300 mg Total in first 24 hours—600-900 mg Oral therapy as soon as possible	Not recommended

* Intravenous infusions in saline glucose saline or plasma

** Winckel[*] recommends concentrated quinine-urethane or quinine antipyrin solutions for intramuscular injection They are nearly neutral in reaction and cause less pain than acid solutions

whereas our knowledge of the use of quinine in these circumstances comes of a vast experience over many years, published information on the use of parenteral chloroquine, though very favourable, is still comparatively small For this information we look to the physicians in tropical countries rather than to the experimental laboratories, and they have still to record a sufficient body of reliable evidence

Intramuscular or intravenous quinine? There is no unanimity on the relative merits of intramuscular and intravenous quinine in malaria Both methods have received authoritative support, though most experienced physicians today seem to favour the intravenous route From the confused evidence the broad facts and opinions which emerge are

(1) that quinine injections should be given only when there are good reasons for them—grave infection, coma, digestive intolerance, defective absorption from the alimentary tract Risks there are, and

though these risks cannot be justified for routine treatment, they must be taken when life is at stake,

(2) that intramuscular quinine always produces tissue necrosis and may leave fibrotic indurations which last for years, that faulty technique may lead to disastrous crippling, or even to death from tetanus, but that with sensible precautions as to the site of injection and the sterility of equipment and solutions these risks are very small,

(3) that intravenous injections of quinine cause a fall in blood-pressure, and carry a small risk of venous thrombosis at the site of injection and a remote risk of sudden death when the injection is given too quickly or when there is quinine hypersensitivity or threatening circulatory failure,

(4) that quinine acts rather more quickly when injected into the blood stream

Intramuscular quinine should be injected deep into the gluteal muscles An injection site about 3 inches (7 5 cm) below the centre of the iliac crest is anatomically safe The skin should be thoroughly cleansed and scrupulous care taken to ensure the sterility of syringe, needle, and solution The ampoules of quinine in concentrated solution prepared by manufacturers for injection are strongly recommended, their sterility is assured, and some of the best of them are especially compounded to give a solution nearly neutral in reaction Single doses should not exceed 1,000 mg (15 grains), and they may with advantage be as small as 500 mg (7½ grains), the total dosage over 24 hours should not exceed 2,000 mg (30 grains) With these precautions, the danger of serious complications is exceedingly small

The cardinal principles of intravenous quinine therapy are high dilution and slow administration Fatalities have occurred from injections given at the rate often recommended—10 minutes for a 20-ml dose containing 650-1,000 mg (10-15 grains) The drug is far better given as a slow intravenous infusion in a litre of saline, glucose saline, or plasma Straban 151 has drawn attention to the efficiency and safety of the continuous intravenous quinine "drip" His experience with grave falciparum infection among ill nourished prisoners of war suggests that the hazards arising from intravenous quinine therapy are much reduced by this method of administration *

* Non-specific therapy is far more important in these grave falciparum infections than in the simple attack For intravenous transfusion the quinine may be given in normal saline glucose saline or plasma some physicians recommend the addition of thiamine or epinephrine or of Pentothal sodium for convulsions or mania Transfusions of fresh blood may be necessary for severe anaemia from heavy destruction of red cells Ransome 1, from his experience with a coma team in Burma during the second World War states that comatose cases do best when nursed in Fowler s position if the state of the circulation is satisfactory

(*b*) *Chloroquine*

The clinical trials of intramuscular and intravenous chloroquine so far reported, though few in number, have been very favourable The drug is said to be safe and effective when given by intravenous injection or infusion, and it has been suggested that intravenous administration might be the method of choice for the initial treatment of the patient who is seriously ill [180] Rapid injection caused dizziness, nausea, disturbance of vision, and a transient fall in blood pressure, but these effects were almost eliminated when the drug was given by infusion in 500 ml of saline The dose was 400 mg of chloroquine base

Several reports have been published recording satisfactory results following intramuscular injections of chloroquine in single doses up to 300 mg of base The injections were well tolerated, and speedy in their effects [175, 176, 181]

Intramuscular and intravenous injections of chloroquine are alike quickly effective, and in the present state of knowledge it seems that intramuscular administration, from its safety and convenience, will usually be the method of choice The patient's state of fluid balance may well be a deciding factor *With obvious dehydration from vomiting, diarrhoea,* or sweating, the clinical advantages of the intravenous infusion or continuous "drip" might outweigh other considerations

(*c*) *Amodiaquine*

Since the two drugs resemble one another so closely as regards their antimalarial activity and toxicity, it seems probable that recommendations for the use of chloroquine in severe malaria will apply equally well to amodiaquine It has been reported that amodiaquine is well tolerated when given intramuscularly and intravenously for simple attacks in doses up to 300 mg of base,[177, 178] but there is little information on its merits for parenteral treatment in severe malaria Until clinical experience has more fully confirmed the efficacy and safety of injections, the drug can be used with confidence for the patient who is seriously ill only when it is possible to give it by mouth

(*d*) *Mepacrine*

Mepacrine is a well proved remedy in severe malaria Like all antimalarial drugs, it is best given by mouth Intramuscular injections of the soluble methanesulfonate are very effective and reasonably safe, intravenous administration is inadvisable as the safety margin is small The dose for a single intramuscular injection should not exceed 300 mg nor the total dose exceed 900 mg for the first 24 hours The drawbacks are those

associated with simple oral therapy, with the added small risk of epileptiform convulsions occurring soon after the injections The convulsions are alarming but they soon pass and seem to have no serious sequelae

3. The relapsing or recrudescent infection

When a malaria infection has been treated and apparently cured, a recurrence of symptoms means that the treatment has either failed to eliminate all the asexual parasites in the blood, or, having cleared the blood completely, has failed to destroy the persisting forms in the fixed tissues Relapses in falciparum infections are attributed to the persistence of a few asexual parasites in the blood despite treatment, they may occur, though not very often, after treatment with any of the 4-aminoquinolines and allied drugs, particularly quinine Relapses in vivax infections, on the other hand, are thought to be due to secondary exoerythrocytic forms which resist the ordinary schizontocidal drugs and survive treatment they are very common after treatment based solely on the 4-aminoquinolines or allied compounds The presumed origin of relapses in malaria may be represented as follows

P falciparum

Primary e-e forms → Asexual blood forms causing primary attack and recrudescences

P vivax

Primary e-e forms → Asexual blood forms causing primary attack
→ Secondary e-e forms → Asexual blood forms causing relapses

The treatment of relapses in malaria recognizes these differences of origin Infection due to *P falciparum* is finally cured by eradication of the asexual blood forms, vivax infections by eradication of both the asexual blood forms and of the secondary exoerythrocytic parasites in the fixed tissues

(a) *Recrudescing falciparum infection*

The asexual blood cycle of *P falciparum* is usually eliminated by the 4-aminoquinolines and similar drugs given at doses appropriate for the acute attack, but falciparum infections do sometimes recrudesce, particularly after quinine treatment They should be treated like any other acute attack, and they may be prevented by a follow up treatment at suppressive dosage with any good schizontocidal drug (See section on after treatment, page 84)

(b) Chloroquine

The clinical
reported, though
said to be safe
infusion, and it
be the method
seriously ill.[180]
vision, and a tr
eliminated when
dose was 400 r

Several rep
following intra
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effects [175, 176, 18

Intramuscul
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"drip" might

(c) Amodiaqui

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antimalarial ac
for the use of
amodiaquine.
given intramu
300 mg of ba
parenteral tre
fully confirme
with confidenc
to give it by r

(d) Mepacrin

Mepacrin
malarial drug
soluble meth
venous adm
dose for a s
total dose e

(...) Relapsing vivax infection

In this case the problem is more difficult. [illegible] ... rarely cured by ordinary schizontocidal treatment [illegible] ... unless this treatment is continued [illegible] ... invasion of the blood stream from [illegible] ... far as we know, is sensitive only to [illegible] ... and, possibly, to pyrimethamine. [illegible] ... based on these drugs. They [illegible] ... moderately toxic, but none [illegible] ... is not well defined; it is not a good [illegible] ... recent work in the United States of America [illegible] ... is possible in some cases treated with [illegible] ... acute attack.[184]

The physician treating a case of [illegible] ... open to him:

(1) To give ordinary schizontocidal treatment [illegible] ... warn the patient of a probable relapse, and [illegible] ... a combination of schizontocide and 8-aminoquinoline.

(2) To follow-up the ordinary schizontocidal treatment [illegible] ... [illegible], chloroquine, amodiaquine, [illegible] ... suppressive dosage, warning the patient [illegible] ... the suppressive drug is withdrawn. This would be [illegible] ... where re-infection is likely, but suppression [illegible] ... period might be necessary.

(3) To treat the primary attack not with schizontocides alone, but ... with a combination of schizontocide * and 8-aminoquinoline.

The [illegible] must be based on the circumstances, [illegible] ... of the patient. A useful compromise for the patient [illegible] ... [illegible] might be somewhat on these [illegible] ... [illegible] schizontocidal drug; follo[illegible] ... [illegible] months; suspend all treatment [illegible] ... [illegible] of schizontocide * and 8-amin[illegible]

[illegible] infection

[illegible] combination of drugs [illegible] ... [illegible] a course of [illegible] ... [illegible] in combination with [illegible] ... [illegible] high proportion [illegible]

this procedure was first suggested by Sinton & Bird[31] in India, who used a combination of pamaquine with quinine This was the standard treatment for the radical cure of vivax malaria until 1945, when primaquine was synthesized by American investigators in the course of their search for a less toxic drug Primaquine appears to be not only less toxic, but also more active than any of the 8 aminoquinolines yet tested The usual course of treatment lasts 14 days, against refractory infections treated at [illegible]

TABLE IX ADULT DOSAGE OF 8-AMINOQUINOLINES FOR RADICAL CURE IN VIVAX INFECTION

Drug	Dosage	
Primaquine base or	15 mg daily for 10-14 days	combined with standard treatment with chloroquine amodiaquine or quinine if an overt attack is in progress
Pamaquine base	8-10 mg thrice daily for 10-14 days	

Radical cure of vivax infections with primaquine may also be attempted
d
s
h
during latency with primaquine alone—15 mg daily for 14 days[43]

Patients taking any of the 8 aminoquinolines should be under daily supervision because of the occasional unpredictable occurrence of acute intravascular haemolysis Cyanosis, abdominal pain, the passage of dark urine, and maybe fever, are the warning signs

4 The dispensary patient

The drug or the treatment best adapted to the needs of the malaria patient in hospital is not necessarily suitable for the dispensary outpatient Dispensary patients report for fever, they will probably wish to return home, and they may not be seen again Treatment must therefore be simple and safe, it must be effective in doses which can be taken at the time of the visit, and it must be cheap The single dose therapy possible with some of the newer drugs meets most of these demands The partial immunity which many of these patients have, particularly in tropical countries, helps the clinical response, and a clinical cure, sometimes a radical cure, may be expected The most useful drugs are chloroquine (Resochin, Nivaquine, Aralen, or Avloclor), and amodiaquine Recommended doses are shown in table X

TABLE X SINGLE DOSE THERAPY FOR DISPENSARY PATIENTS

Drug	Dosage (mg) and age (years)					
	adult	over 12	6-12	3-6	1-3	under 1
Chloroquine or	600 base	450-600	450	300	225	37 75
Amodiaquine	600 base	400-600	400	300	200	100-150

Single dose treatment with proguanil has proved effective in certain countries and good results have also been reported with pyrimethamine given in the same manner In view of the possibility of drug resistance arising with both proguanil and pyrimethamine, it seems wiser to reserve these drugs exclusively for prophylaxis and suppression

Single doses of mepacrine sometimes fail, and single doses of quinine usually fail These drugs are hence unsuitable for single dose therapy They should be used only when no other drugs are available and then be given over several days The doses recommended for adults are shown in table XI

TABLE XI ADULT DOSAGE OF MEPACRINE AND QUININE FOR DISPENSARY PATIENTS

First dose at dispensary	6 hours later	Daily for the next 3 days
Mepacrine—400 mg	200 mg	300 mg (in one dose)
Quinine salt—1 000 mg (15 grains)	1 000 mg (15 grains)	1 500 mg (23 grains) (in divided doses)

5 After treatment

The primary aim of the treatment recommended for the simple, the grave, and the relapsing infection, is the speedy and safe cure of the attack, with such permanence as is possible with modern drugs given at practical dosage Specific after treatment ensures that the patient is not infective to mosquitos when he leaves hospital, and raises the odds of permanent cure

(a) *Falciparum infection*

Radical cure is probable with any of the schizontocidal treatments recommended for the acute attack, but freedom from early relapses may be further assured by a ' follow up " regimen continuing for one month at suppressive dosage chloroquine base—300 mg weekly, amodiaquine

base—400 mg weekly, proguanil salt—100 mg daily, or pyrimethamine—25 mg weekly (See also section 3, (a))

In cases where it is considered desirable to sterilize the gametocytes, specific after treatment is necessary, for the 4-aminoquinolines and similar drug [illegible] pam [illegible] for [illegible] treatment may begin when the temperature has fallen to normal or at the end of schizontocidal treatment, depending on the clinical condition of the patient Delay is perhaps wise if the patient has been seriously ill, for primaquine and pamaquine contribute nothing to recovery and the slight hazard of early combined therapy serves no useful purpose

(b) *Vivax infection*

Suppressive after treatment which will give the patient an assured freedom from a recurrence of fever, at least for a time is recommended when the attack has been treated with schizontocidal drugs alone Suitable drugs and doses are pyrimethamine—25 mg weekly, proguanil salt—100 mg daily, chloroquine base—300 mg weekly amodiaquine base—400 mg weekly, or mepacrine—100 mg daily Suppressive therapy may conveniently begin ten days after the completion of treatment for the attack, and continue for two months Whether suppression for a longer period is justified must depend on the circumstances of the patient (See also section 3, (b) and (c))

6 **Blackwater fever**

In the early stages of blackwater fever, malaria parasites may be found in about half the cases but as haemolysis proceeds they often disappear When parasites are demonstrable in the blood, chloroquine, proguanil, or mepacrine should be given at normal dosage if parasites are not found, suppressive therapy should be maintained into convalescence and a full course given when the clinical condition of the patient justifies it Quinine, pamaquine, and primaquine are contraindicated

The Symptomless Carrier

The malaria carrier who has no symptoms poses a variety of problems for which chemotherapy today often has an appropriate answer, but the answer may be determined more by circumstances than by the status of the individual infection Broadly, three courses are open to cure the infection, to suppress it, or to let it burn out'

1 *The latent vivax infection*

Curative therapy is desirable if the patient is not exposed to re infection, and if it is practical under the patient's particular conditions of life Primaquine—or, if this is unobtainable, pamaquine—should be given at full dosage without a schizontocide The marginal toxicity of these drugs and the need for supervision are limiting factors If curative treatment is inexpedient, suppression is the best alternative Pyrimethamine, at a dosage of 25 mg once a week, is probably the best suppressive drug, continued for at least eight weeks it may sometimes result in suppressive cure Sometimes these infections may be left to burn themselves out Most physicians in the tropics have seen highly refractory vivax infections which resist all curative treatment They have then to decide whether to suppress the infections indefinitely, or to leave the patient to work out his own salvation, protected only by schizontocidal treatment for late attacks

2 *The "blood positive" carrier*

Curative therapy or suppression are the alternatives, with gametocyte therapy in addition for "crescent" carriers Circumstances will decide the appropriate course Curative therapy is indicated when re-infection is unlikely

3 *The patient with splenic enlargement*

Parasites may or may not be demonstrable in the blood of the symptomless patient with an enlarged malarial spleen These patients are usually semi-immunes in endemic areas Suppressive therapy, efficiently applied over a few months, will markedly reduce the size of most malarial spleens

Individual Drug Prophylaxis

Simple though the concept of malaria prevention by drugs may be, the application of preventive therapy to the varied needs of the person exposed to, or infected with, the malaria parasite is far from simple If an individual wishes to live in a malarious country and remain healthy, he will ask to be protected against all forms of malaria He may wish for protection to cover a short exposure, with protective therapy nicely timed to the period of risk, or for continuous protection during prolonged exposure, if infected, he will ask to be cured, or at least protected from the clinical manifestations of infection Most of these demands can be met by use of the drugs now available

1 *General protection*

The suppression of symptoms is perhaps the most useful clinical benefit conferred by regular and prolonged administration of small doses of antimalarial drugs, but it is not the only benefit Some infections are cured, and with particular drugs some are eradicated before they reach the blood stream The term *general protection* is used here to include suppression, suppressive cure, and causal prophylaxis The drugs commonly used are listed in table XII Given at the dosage recommended these drugs are efficient suppressives in all forms of malaria, and, with the possible exception of quinine, they are all likely to cure falciparum infection within about a month Proguanil and pyrimethamine in addition will usually eradicate falciparum infection at its source in the fixed tissues None of these drugs is likely to eradicate vivax infection with the possible exception of pyrimethamine, which appears to have achieved suppressive cure in some cases against a particular strain of parasite

TABLE XII DOSAGE OF VARIOUS DRUGS FOR GENERAL PROTECTION

Drug	Interval	Dosage (mg) and age (years)					
		over 16	11 16	7 10	4-6	1-3	under 1
Proguanil salt * or	daily	100	100	75	50	50	25
Chloroquine base	weekly	300	225	150	100	75	37
Amodiaquine base or	weekly	400	300	200	133	100	—
Mepacrine ** or	daily	100	75	50	25	—	—
Pyrimethamine * or	weekly	25	25	18	12	6	—
Quinine salt †	daily	500-650 (8-10 grains)	300-500 (5 8 grains)	200-250 (3-4 grains)	130-200 (2-3 grains)	130 (2 grains)	65 (1 grain)

When protection is required for a limited period only drug administration should be continued for one week after the last day of exposure in the case of proguanil and pyrimethamine and for one month in the case of all other drugs

* Contraindicated in areas where the prevailing malaria is known to be resistant to either of these drugs

** Beginning 10 days before exposure to infection With the other drugs listed it is unnecessary to begin the course earlier than the first day of exposure

† Recommended only when other drugs are not available

Of the drugs listed, proguanil is a causal prophylactic against falciparum infection, and is a good suppressive and an active sporontocide in all forms of malaria, its toxicity is very low Its tendency to provoke resistance has been discussed in chapter 4 (page 59) In parts of Africa

the doses recommended in table XII have proved insufficient for clinical protection, and double this dosage may be necessary in such areas

Chloroquine and amodiaquine are *powerful suppressants* and will achieve suppressive cure in falciparum infection, their toxicity is low, and they do not provoke drug resistance They are inactive against the pre erythrocytic forms of *P falciparum* and have no inhibitory effect on sporogony

Mepacrine resembles chloroquine and amodiaquine *in its clinical range* but is somewhat less active and not entirely free from toxic side effects Though a thoroughly reliable drug for clinical protection, it can no longer be recommended when the more effective 4-aminoquinolines are available

Pyrimethamine has very much the same activity as proguanil, but in addition will sometimes achieve suppressive cure with certain strains of *P vivax*, its toxicity is low Its tendency to provoke resistance has been discussed in chapter 4 (page 58)

Quinine, though a useful drug for clinical protection and still highly regarded in some countries by persons of conservative habit, is less efficient than the synthetic compounds mentioned above and can be recommended only when these are not available Its mode of action resembles that of the 4-aminoquinolines and of mepacrine

2 *Causal prophylaxis*

With some of the modern drugs it is possible to eradicate malaria infections at their source in the fixed tissues, but the application, in the field and in hospital practice, of this radical form of prevention (the *causal prophylaxis* of James) *is restricted* by specific differences in the parasites and by the toxicity of some of the drugs The prospects in falciparum malaria are very good, in vivax malaria they are poor, while in malariae and ovale malaria they are not fully known Proguanil and *pyrimethamine* given at the doses listed in table XII are safe and highly efficient causal prophylactics in falciparum infection, failing only with strains which are resistant to these drugs But all the drugs listed are comparatively inert against the pre erythrocytic forms of *P vivax*, and causal prophylaxis in vivax infections has been attained only with the 8 aminoquinolines, particularly pamaquine and primaquine Given at about the time of the infecting bite, pamaquine and primaquine will eradicate infection at the source, but the time of the *infecting bite is seldom known* and both drugs are too toxic for prolonged administration

3 *Toxicity of antimalarial drugs*

Any drug which has to be taken over a long period must be free from serious side-effects At the dosage appropriate for prophylaxis, proguanil

is non toxic, pyrimethamine, given continuously in doses of the order of 25 mg daily, has a reversible depressive effect on the bone marrow, but the dose recommended for prophylaxis is so extremely small that the risk of toxic effects is remote, chloroquine and amodiaquine carry no known risk of any consequence Mepacrine stains the skin and conjunctivae, and sometimes causes a lichenoid dermatitis, while psychoses occurring during suppressive administration have been reported Quinine has a wide margin of safety, but sometimes causes unpleasant cinchonism More detailed information regarding the toxicity of individual compounds is given in chapter 3 All in all, the risks of harmful side-effects from prophylaxis based on these drugs are small, particularly when they are assessed in the light of the benefits the drugs confer Only with mepacrine and quinine are these effects ever likely to discourage wide scale use

Collective Drug Prophylaxis

Malaria in a community reflects a biological relationship between malaria parasites, their human hosts, and the mosquitos which bring them together Eliminate the mosquitos, or break their contact with man, and malaria disappears most large-scale malaria-control projects take advantage of these facts Eliminate the parasites, or interrupt their life-cycle at

stances it may be almost complete

1 *Principles*

So long as personal drug prophylaxis is restricted to a few individuals, its effect on the malaria of the community to which they belong will be incidental and probably small But when personal prophylaxis is spread so widely as to become collective prophylaxis a new series of effects, cumulative and highly significant for the community, contribute to the reduction or elimination of the seed bed from which the mosquitos derive their infection Personal drug prophylaxis depends essentially on the interruption of the asexual cycles of the parasite, collective drug prophylaxis brings into play an additional action on gametogony and sporogony, with an interruption in the transmission of infection to mosquitos The factors

Suppression by chloroquine

Effect on asexual blood cycle	*Collateral effect on gametocyte reservoir*
(a) Suppressive cure of falciparum infection	None at first, later, with cessation of attacks, no further production
(b) Suppression of vivax and malariae infection	Existing gametocytes destroyed, with cessation of attacks no further production

Causal prophylaxis and suppression by proguanil

Effect on asexual cycles in blood and tissues	*Collateral effect on gametocyte reservoir*
(a) Prevention of falciparum infection	No production
(b) Suppressive cure of existing falciparum infection	Sporogony inhibited, with cessation of attacks, no further production of gametocytes
(c) Suppression of vivax and malariae infection	

Since amodiaquine and mepacrine resemble chloroquine in their effects, whilst pyrimethamine in most respects resembles proguanil, these drugs given efficiently to every member of a closed community might be expected on theoretical grounds to arrest transmission completely, but practical difficulties limit their effect Communities are seldom isolated from outside sources of infection, and the administration of any drug with unfailing regularity to every member of a community is an exacting task The collateral effects of collective drug prophylaxis on the transmission of infection will hence be related to the epidemiological situation, and to the proportion of the community under regular drug protection

2 *Drugs and dosage*

The continuous administration of a good schizontocide to a whole population, with dosage intervals related to the potency and persistence of the drug in the body, is theoretically the most effective method of collective drug prophylaxis Initial "mass" or "blanket" therapy at a dosage appropriate for acute attacks is sometimes recommended but is seldom necessary Other methods of administration—intermittent "mass" or "blanket" treatments at intervals of weeks or months, and selective treatments for parasite carriers—have usually been less successful Collective drug prophylaxis based on pamaquine has been generally abandoned, but the possibilities in this field of the more active and less toxic 8 aminoquinoline, primaquine, have yet to be defined

For the community, as for the individual, the most suitable drugs are proguanil, chloroquine, amodiaquine, mepacrine, and pyrimethamine Table XIII summarizes the dosage recommended

TABLE XIII. ADULT DOSAGE OF VARIOUS DRUGS USED FOR COLLECTIVE PROPHYLAXIS*

Drug	Communities with little immunity, armies in the field, etc	Communities in endemic areas
Proguanil[a, b], or	100 mg salt daily	200 mg salt twice a week or 300 mg salt once a week
Chloroquine, or	300 mg base once a week	300 mg base once in 1-2 weeks
Amodiaquine or	400 mg base once a week	400 mg base once in 1-2 weeks
Mepacrine or	100 mg daily	200 mg twice a week or 300 mg once a week
Pyrimethamine,[a] or	25 mg once a week	25 mg once a week
Quinine[c]	650 mg (10 grains) daily	300 mg (5 grains) daily

* The doses for children are summarized in table XII

[a] Contraindicated in areas where the prevailing malaria is known to be resistant to *either* of these drugs

[b] A daily dose of 200 mg has been found necessary in parts of Africa

[c] Recommended only when other drugs are not available

3 *Indications for collective drug prophylaxis*

The most successful and indeed the only lasting methods of malaria control in stable communities are those which depend on action against the insect vectors There is little or no evidence that malaria can be completely and permanently controlled by drugs But mosquito control is

tions:

(*a*) that mosquito control is the most successful form of permanent malaria control,

(*b*) that collective drug prophylaxis is always the method of choice for mobile groups operating in malarious country;

(*d*) that the application of collective drug prophylaxis in stable popu lations is justified only when more permanent methods are impracticabl or disappointing

Collective drug prophylaxis has important limitations It is likely to be successful only when the regularity of administration can be assured, and it is justified only when the malaria cannot be controlled at comparable trouble and expense by measures directed against the mosquito Adequate supervision for the administration of drugs is possible only in populations which are fairly concentrated and under some form of discipline, such as armies in the field, labour gangs operating in malarious country, or plantation populations, and it is in these groups that collective drug prophylaxis achieves its most satisfying results

The possibilities of collective drug prophylaxis in rural communities are less impressive It can seldom be efficiently applied and is beset with administrative and other difficulties, it remains, however, the quickest method of bringing an epidemic under temporary control

4 *Control of epidemics*

Severe epidemic malaria demands quick action many people are sick, a few maybe are dying, and the immediate situation can be met by drugs alone Collective drug prophylaxis, starting with a loading dose, has here one of its clearest indications The drugs and doses recommended are summarized in table XIV

TABLE XIV ADULT DOSAGE OF VARIOUS DRUGS FOR THE EMERGENCY CONTROL OF EPIDEMIC MALARIA

Immediate single dose	Follow up continuous dosage
Chloroquine—600 mg base or	Chloroquine—300 mg base weekly or
Amodiaquine—600 mg base	*Amodiaquine—400 mg base weekly or*
If these drugs are not available use	Proguanil *—100 mg salt daily or
	Mepacrine—100 mg daily or
Mepacrine—400 mg	Pyrimethamine*—25 mg weekly

* Contraindicated in areas where the prevailing malaria is known to be resistant to *either* of these drugs

For individuals with fever at the time of examination, a single dose of chloroquine, amodiaquine or mepacrine is sometimes inadequate, further treatment with 300 mg daily for two days is desirable The persons distributing the drugs should ensure that the full dose is swallowed and washed down with a drink of water This precaution, a wise one at all times in collective drug prophylaxis, has a special importance during epidemics

When the malaria is under control, a reduction of the follow up dosage of proguanil or mepacrine to 200 mg twice a week, or 300 mg once a week, may be considered Drug administration should continue for at least one month—long enough for a suppressive cure of most falciparum infections The likelihood of recrudescent vivax and malariae infections occurring some weeks after discontinuing the drugs should not be forgotten

The emergency distribution of drugs should not replace or delay other and more lasting forms of control House-spraying with residual insecticides should begin at once, and steps be taken to ascertain the cause of the epidemic Whether drugs should or should not play any part in future control policy must depend on the prevailing conditions and available resources

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ANNEXES

ANNEX 1

SUMMARY OF SUGGESTED DOSAGE

Note The doses suggested in this summary are for adults of approximately 150 lb (70 kg) body-weight In general they should be adjusted according to the usual rules for weight and age The doses recommended for prophylaxis and suppression in children are given in table XII.

Treatment of clinical attack in non immune subjects

(1) Chloroquine diphosphate or sulfate 600 mg of base, 300 mg 6 hours later; 300 mg daily for next 2 days, OR

(2) Amodiaquine dihydrochloride dihydrate 600 mg of base first day, 400 mg daily for next 2 days, OR

(3) Mepacrine dihydrochloride dihydrate 1,000 mg (5 doses of 200 mg) first day, 100 mg thrice daily for next 6 days, OR

(4) Quinine sulfate or dihydrochloride 1,300-2,000 mg (20-30 grains) daily for 5-7 days

Emergency treatment

(1) Quinine dihydrochloride 650 mg (10 grains) in normal saline, glucose saline, or plasma, injected intravenously *very slowly* (not more than 50 mg of salt per minute), repeated in 6 hours if necessary, not more than 3 injections in 24 hours *Or* administered by intravenous drip, at the rate of 2,000 mg (30 grains) in 24 hours Oral therapy as soon as possible, OR

(2) Mepacrine methane sulfonate given intramuscularly in single doses not exceeding 300 mg, total in first 24 hours, 600-900 mg Oral therapy as soon as possible, OR

[illegible]

the intramuscular route, which is generally to be preferred Oral therapy as soon as possible

Radical cure of vivax and malariae infection

(1) Primaquine diphosphate 15 mg of base daily in single or divided doses, for 14 days, reinforced by standard treatment with a schizontocidal drug * if given during an acute attack, OR

(2) Pamaquine naphthoate or monohydrochloride 8 10 mg of base thrice daily for 10-14 days, reinforced by standard treatment with a schizontocidal drug * if given during an acute attack

* Mepacrine should not be given *concurrently* with any of the 8-aminoquinoline drugs

Treatment of clinical attack in semi immune subjects

(1) Chloroquine diphosphate or sulfate 600 mg of base, single dose; OR

(2) Amodiaquine dihydrochloride dihydrate 600 mg of base, single dose, OR

(3) Mepacrine dihydrochloride dihydrate 400 mg, 200 mg 4 hours later, 300 mg daily for next 3 days, OR

(4) Quinine sulfate or dihydrochloride 1,000-1,500 mg (15 23 grains) daily for 2-5 days

Prophylaxis and suppression *

(1) Chloroquine diphosphate or sulfate 300 mg of base once weekly, OR

(2) Proguanil monohydrochloride ** 100 mg daily,† *or*, for partially immune subjects, 300 mg once weekly, OR

(3) Amodiaquine dihydrochloride dihydrate 400 mg of base once weekly, OR

(4) Pyrimethamine ** 25 mg once weekly, OR

(5) Mepacrine dihydrochloride dihydrate 100 mg daily, *or*, for partially immune subjects, 300 mg once weekly *Administration beginning 10 days before exposure to infection*, OR

(6) Quinine sulfate or dihydrochloride 650 mg (10 grains) daily *Recommended only when none of the above listed drugs is available*

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* The prophylactic regimen should be continued for one week after leaving an endemic area where proguanil or pyrimethamine has been used and for one month in the case of other drugs

** The use of proguanil or pyrimethamine is contraindicated in areas where resistance to *either* of these drugs is known to exist

† In parts of Africa this dosage has been found insufficient in Nigeria, for instance the following scale has been recommended adults, 100-200 mg daily, children 0-1 year 50 mg three to six times weekly 1 3 years 50 mg daily, over 3 years 100 mg daily

ANNEX 2

BASE-CONTENT OF TABLETS

Each 261 mg tablet of amodiaquine dihydrochloride dihydrate salt contains 200 mg of base

Each 250-mg tablet of chloroquine diphosphate salt contains 150 mg of base

Each 500-mg tablet of chloroquine diphosphate salt contains 300 mg of base

Each 204-mg tablet of chloroquine sulfate salt contains 150 mg of base

Each 136 mg tablet of chloroquine sulfate contains 100 mg of base

Each 408 mg tablet of chloroquine sulfate contains 300 mg of base

Each 100-mg tablet of mepacrine dihydrochloride dihydrate contains 78 5 mg of base

Each 360-mg ampoule of mepacrine methanesulfonate contains the equivalent of 300 mg of mepacrine dihydrochloride dihydrate

Each 120-mg ampoule of mepacrine methanesulfonate contains the equivalent of 100 mg of mepacrine dihydrochloride dihydrate

Each 18 mg tablet of pamaquine naphthoate 10-mg tablet of pamaquine dihydrochloride or 9 mg tablet of pamaquine monohydrochloride contains 8-mg of base For practical purposes 2 naphthoate = 1 base = 1 mono- or dihydrochloride

Each 13 2 mg tablet of primaquine diphosphate contains 7 5 mg of base

Each 100-mg tablet of proguanil monohydrochloride contains 87 mg of base

Pyrimethamine is prescribed in the form of base, *not* as a salt

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ANNEX 3

PHYSICAL DATA REGARDING SALTS

Drug	*Salt*	*Base-content (%)*	*Solubility in cold water * (g per 100 ml)*	*Stable or unstable in aqueous solution*
Quinine	sulfate	82 84	0 125	stable
	bisulfate	58-62	10	stable
	dihydrochloride	79-82	167	stable
	hydrochloride	81-83	3 1	stable
Chloroquine	diphosphate	62	at least 100	stable
	sulfate	76 5	33 3	stable
	hydrochloride	90	33.3	stable
Amodiaquine	dihydrochloride dihydrate	75 8	at least 20	unstable
Mepacrine	dihydrochloride dihydrate	78 5	2 5	unstable
	dimethanesulfonate	65 5	33.3	stable but should not be stored for any length of time
Proguanil	monohydrochloride	86	1	stable
Pyrimethamine	base	100	insoluble	—
Pamaquine	naphthoate	45	insoluble	—
	monohydrochloride	*89 5*	*at least 20*	stable but should be stored under inert gas and in the dark
Primaquine	diphosphate	57	at least 100	stable but some decomposition may take place on exposure to air and light

* i.e., 20° C

Annex 4

SYNONYMS OF ANTIMALARIAL DRUGS

Amodiaquine

CAM-AQ1
Cam-aqi
Camoquin
Flavoquine
Miaquin
SN 10751

Chloroquine

* Aralen
* Avloclor
** Nivaquine B
Resochin
Tanakan
SN 7618
3377 RP

Mepacrine

Acriquine
Arichin
Atabrine
Atatrin
Atebrin
Atebrine
Chemiochin
Chinacrin
Chinacrine
Crinodora
Erion
Haffkinine
Italchina
Malaricida
Methoquine
Metoquina
Metoquine
Palacrin
Palusan
Quinacrine
SN 390

Pamaquine

Aminoquin
Beprochin
Gamefar
Pamaquin
Plasmochin
Plasmoquine
Praequine
SN 971

Primaquine

SN 13272

Proguanil

Bigumal
Chlorguanide
Chloriguane
Diguanyl
Drinupal
Guanatol
Paludrine
Palusil
Tirian
M 4888
SN 12837

Pyrimethamine

Daraprim
Malocide
B-W 50-63

Sontoquine

Nivaquine A
Nivaquine C
Santochin
Santoquine
Sontochin
SN 6911
3038 RP

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* Aralen and Avloclor are chloroquine diphosphate
** Nivaquine B, or Nivaquine, is chloroquine sulfate

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